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=> s l2 and BMP
L3         2334 L2 AND BMP

=> s l3 and "MP52"
L4            0 L3 AND "MP52"

=> s l3 and "GDF-5"
L5           34 L3 AND "GDF-5"

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L6           17 DUP REMOVE L5 (17 DUPLICATES REMOVED)

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L6   ANSWER 1 OF 17     MEDLINE                          DUPLICATE 1
2001271812  Document Number: 21221086.    PubMed ID: 11320249.   Mutation in
     bone morphogenetic protein receptor-IB is
     associated with increased ovulation rate in Booroola Merino ewes. Mulsant
     P; Lecerf F; Fabre S; Schibler L; Monget P; Lanneluc I; Pisselet C; Riquet
     J; Monniaux D; Callebaut I; Cribiu E; Thimonier J; Teyssier J; Bodin L;
     Cognie Y; Chitour N; Elsen J M. (Institut National de la Recherche
     Agronomique, Laboratoire de Genetique Cellulaire, BP, 27, 31326
     Castanet-Tolosan, France.. mulsant@toulouse.inra.fr) . PROCEEDINGS OF THE
     NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2001 Apr
     24) 98 (9) 5104-9.  Journal code: PV3; 7505876. ISSN: 0027-8424. Pub.
     country: United States. Language: English.
AB   Ewes from the Booroola strain of Australian Merino sheep are characterized
     by high ovulation rate and litter size. This phenotype is due to the
     action of the FecB(B) allele of a major gene named FecB, as determined by
     statistical analysis of phenotypic data. By genetic analysis of 31
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informative half-sib families from heterozygous sires, we showed that the FecB locus is situated in the region of ovine chromosome 6 corresponding to the human chromosome 4q22-23 that contains the **bone morphogenetic protein** receptor IB (BMPR-IB) gene encoding a member of the transforming growth factor-beta (**TGF-beta**) receptor family. A nonconservative substitution (Q249R) in the BMPR-IB coding sequence was found to be associated fully with the hyperprolificacy phenotype of Booroola ewes. In vitro, ovarian granulosa cells from FecB(B)/FecB(B) ewes were less responsive than granulosa cells from FecB(+)/FecB(+) ewes to the inhibitory effect on steroidogenesis of **GDF-5** and **BMP-4**, natural ligands of BMPR-IB. It is suggested that in FecB(B)/FecB(B) ewes, BMPR-IB would be inactivated partially, leading to an advanced differentiation of granulosa cells and an advanced maturation of ovulatory follicles.

L6 ANSWER 2 OF 17 SCISEARCH COPYRIGHT 2002 ISI (R)

2001:775367 The Genuine Article (R) Number: 473PK. **Bone morphogenetic proteins** in the development and healing of synovial joints. Edwards C J (Reprint); Francis-West P H. Tan Tock Seng Hosp, Dept Rheumatol Allergy & Immunol, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore (Reprint); Univ London Imperial Coll Sci Technol & Med, Sch Med, Kennedy Inst Rheumatol, London, England; Univ London Kings Coll, Dept Craniofacial Dev, London WC2R 2LS, England. SEMINARS IN ARTHRITIS AND RHEUMATISM (AUG 2001) Vol. 31, No. 1, pp. 33-42. Publisher: W B SAUNDERS CO. INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA. ISSN: 0049-0172. Pub. country: Singapore; England. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Objectives: To review current knowledge of the role of **bone morphogenetic proteins** (**BMPs**) in joint formation and how this may be relevant to healing in adult joints.

Method. Review of published literature using a search of the PubMed database (1966 to 2000) made available by the National Library of Medicine. Additional articles of historical interest were identified from the bibliographies of published literature.

Results: **BMPs** and a related family, the growth and differentiation factors (GDFs), are stimulators of bone and cartilage formation in the developing skeleton. They, together with their antagonists, play key roles in the specification of the joint site and cavitation of synovial joints during embryonic development. Disruption of the **GDF-5** gene in mice and humans is associated with abnormal joint formation. In situ hybridization studies have shown that **BMPs** are expressed during formation of synovial joints in the embryo. However, excessive **BMP** activity leads to obliteration of joints because of cartilage overgrowth. **BMPs** are being considered as therapeutic agents to stimulate healing of articular cartilage after damage. Evidence suggests that **BMPs** are present in adult joints and have roles in healing and maintenance. However, inflammatory cytokines and growth factors present in damaged joints modulate the actions of **BMPs**.

Conclusions: **BMPs**, and in particular **GDF-5**, are involved in synovial joint formation. They may also have effects on the maintenance and healing of adult joints, but factors present after damage may alter their effectiveness.

Relevance: Articular cartilage heals poorly after damage. **BMPs** may be useful therapeutically to stimulate healing of damaged articular cartilage. Increased knowledge of their role in joint formation will improve understanding of how to use them. Copyright (C) 2001 by W.B. Saunders Company.

L6 ANSWER 3 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2

2000:472896 Document No.: PREV200000472896. Inductive activity of recombinant human growth and differentiation factor-5. Spiro, R. C. (1); Liu, L.-S.; Heidaran, M. A.; Thompson, A. Y.; Ng, C. K.; Pohl, J.; Poser, J. W.. (1)

Orquest, Inc., 365 Ravendale Drive, Mountain View, CA, 94043 USA. Biochemical Society Transactions, (2000) Vol. 28, No. 4, pp. 362-368. print. ISSN: 0300-5127. Language: English. Summary Language: English.

AB Growth and differentiation factor-5 (**GDF-5**) is a divergent member of the transforming growth factor-beta/**bone morphogenetic protein** (**BMP**) superfamily that is required for proper skeletal patterning and development in the vertebrate limb. Based on the homology of **GDF-5** with other bone-inducing **BMP** family members, the inductive activity of a recombinant form of human **GDF-5** (rhGDF-5) was evaluated in a series of in vitro assays and in vivo bone-formation models. The in vitro response to rhGDF-5 resulted in the formation of chondrogenic nodules in fetal rat calvarial cells cultured in the context of collagen or collagen/hyaluronate extracellular matrices. Matrices loaded with rhGDF-5 induced ectopic cartilaginous and osseous tissue when implanted in subcutaneous or intramuscular sites. In non-human primate long-bone-defect and spinal-fusion models, rhGDF-5 combined with a mineralized collagen matrix induced bone formation in a manner equivalent to autogenous bone. These results highlight the unique potential of rhGDF-5 in a wide variety of orthopaedic applications.

L6 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2002 ACS

2001:140581 Document No. 134:276100 Extracellular matrix modulation of rhGDF-5 induced cellular differentiation. Heidaran, Mohammad A.; Daverman, Robin; Thompson, Andrea; Ng, Chee Keng; Pohl, Jens; Poser, James W.; Spiro, Robert C. (Orquest, Inc., Mountain View, CA, USA). e-biomed [online computer file], 1, 121-135 (English) 2000. CODEN: EBIOF4. ISSN: 1524-8909. URL: http://pinkerton.catchword.com/vl=80279380/cl=20/nw=1/fm=docpdf/rpsv/catchword/mal/15248909/v1n9/s21/p121.idx Publisher: Mary Ann Liebert, Inc..

AB Growth and differentiation factor-5 (**GDF-5**) is a divergent member of the **TGF-.beta./bone morphogenetic protein** (**BMP**) superfamily that is required for proper skeletal patterning and joint development in the vertebrate limb. Based on the homol. of **GDF-5** to other bone-inducing **BMP** family members, the inductive activity of a recombinant form of human **GDF-5** (rhGDF-5), and the influence of the extracellular matrix (ECM) on this inductive activity was evaluated in a series of well-defined in vitro assays. Fetal rat calvarial (FRC) cells were plated on various purified extracellular matrix proteins in the presence of rhGDF-5 (100 ng/mL) for 3 wk and scored for differentiation at the level of morphol., overall proteoglycan synthesis and deposition, aggrecan and Type II collagen mRNA and protein expressions. Results show that **GDF-5** stimulated chondrogenic nodule formation by FRC cells plated on Type I collagen but to a lesser extent on tissue culture plastic or fibronectin. These chondrogenic nodules stained heavily with Alcian blue and expressed chondrogenic markers such as Type II collagen and aggrecan, as judged by immunohistochem. and RT-PCR analyses, resp. Cells in the monolayer that surrounded the nodules did not express the chondrogenic markers. The mol. signaling mechanism by which **GDF-5** induces chondrogenesis modulators of intracellular signaling mediators. Results show that the ligand-dependent chondrogenesis was inhibited by the calcium ionophore A23187, rapamycin but not by dibutyryl-cAMP, Na3/VO4, or EGTA. The known effects of A23187 and rapamycin on intracellular signaling pathway suggest that the **GDF-5**/Type I collagen-induced chondrogenesis is mediated through modulation of intracellular calcium concn. accompanied by activation of the p70 S6 kinase (p70s6k) signaling pathway. Together, these results indicate that cellular interaction with Type I collagen significantly enhances the differentiating activity of **GDF-5**. This effect is likely mediated by the convergence of downstream matrix and growth factor receptor signaling pathways.

L6 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2002 ACS

1999:404996 Document No. 131:39712 Methods for maintaining or restoring tissue-appropriate phenotype of soft tissue cells by altering morphogen-activated regulatory pathways. Sampath, Kuber T.; Cohen, Charles M.; Oeda, Eiichi; Miyazono, Kohei; Kawabata, Masahiro (Creative Biomolecules, Inc., USA). PCT Int. Appl. WO 9931136 A2 19990624, 50 pp. DESIGNATED STATES: W: AU, CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US26788 19981216. PRIORITY: US 1997-69931 19971217; US 1998-110498 19981201.

AB Methods for maintaining or restoring tissue-appropriate phenotype of diseased, damaged, or aged mammalian soft tissue cells and methods for treating disorder characterized by a decreased level of endogenous expression of a morphogen are disclosed. The methods of the invention serve to manipulate any one or several aspects of morphogen-activated regulatory pathways of phenotype-specific protein expression. Thus, the biol. effects of different Smad proteins were examd. in C2C12 undifferentiated mesenchymal cells using an adenovirus-based vector system. Pathway-restricted Smads (R-Smads) activated by **BMP** receptors, such as Smad1 and Smad5, induced the prodn. of alk. phosphatase in C2C12 cells, whereas the R-Smads activated by the **TGF**-**beta**./activin pathway (Smad2 and Smad3) did not. Addn. of **BMP**-6 dramatically enhanced the prodn. of alk. phosphatase induced by Smad1 or 5 which may be due to the nuclear translocation of R-Smads induced by **BMP**-6. **BMP** type 1 receptors such as ALK-3, ALK-6 and ALK-2, which are known to activate Smad1 and 5, also induced the prodn. of alk. phosphatase, in these cells. Anti-Smads, i.e., Smad6 and Smad7, inhibited the prodn. of alk. phosphatase induced by Smads 1 and 5.

L6 ANSWER 6 OF 17 SCISEARCH COPYRIGHT 2002 ISI (R)

1999:777722 The Genuine Article (R) Number: 243VL. Minimal promoter components of the human growth/differentiation factor-5 gene. Sugiura T (Reprint); Hotten G; Kawai S. DAIICHI PHARMACEUT CO LTD, TOKY R&D CTR, BASIC TECHNOL RES LAB, EDOGAWA KU, 16-13 KITA KASAI 1 CHOME, TOKYO 1348630, JAPAN (Reprint); HOECHST MARION ROUSSEL LTD, DISCOVERY RES LABS, LAB BONE RES, KAWAGOE, SAITAMA 3501165, JAPAN; BIOPHARM GMBH, D-69115 HEIDELBERG, GERMANY. BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS (5 OCT 1999) Vol. 263, No. 3, pp. 707-713. Publisher: ACADEMIC PRESS INC. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0006-291X. Pub. country: JAPAN; GERMANY. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Growth/differentiation factor-5 (**GDF**-**5**) is a new member of the **BMP** family supposed to be involved in chondrogenesis. We cloned the human **GDF**-**5** gene from lambda phage library and sequenced its 3.5-kb 5'-flanking region. The transcription start site was mapped by 5'-RACE to the sequence that coincides with the initiator element. Electrophoresis mobility shift assays (EMSA) demonstrated a zinc finger transcription factor, YY1, to bind to the sequence surrounding the transcription start site. To localize positive and negative regulatory elements in the **GDF**-**5** 5'-upstream region, we constructed a series of progressively deleted promoter-reporter plasmids. The transient transfection assay with human osteoblastic Hos cells indicated that a minimal enhancer element resides within -117 to -27 relative to the transcription initiation site. Since the **GDF**-**5** promoter was active even in fibroblastic L cells, a mechanism governing its chondrocyte-restrictive expression needs to be explored. (C) 1999 Academic Press.

L6 ANSWER 7 OF 17 MEDLINE DUPLICATE 3

1999343659 Document Number: 99343659. PubMed ID: 10413589. p38 mitogen-activated protein kinase functionally contributes to chondrogenesis induced by growth/differentiation factor-5 in ATDC5 cells. Nakamura K; Shirai T; Morishita S; Uchida S; Saeki-Miura K; Makishima F. (Discovery Research Laboratories, Hoechst Marion Roussel Ltd., 3-2, Minamidai 1-chome, Kawagoe, Saitama, 350-1165, Japan.) EXPERIMENTAL CELL RESEARCH, (1999 Aug 1) 250 (2) 351-63. Journal code: EPB; 0373226. ISSN:

0014-4827. Pub. country: United States. Language: English.

AB Recent studies of intracellular signal transduction mechanisms for the transforming growth factor-beta (**TGF-beta**) superfamily have focused on Smad proteins, but have paid little attention to mitogen-activated protein (MAP) kinase cascades. Here we demonstrate that growth/differentiation factor-5 (**GDF-5**), but neither **bone morphogenetic protein**-2 (**BMP**-2) nor TGF-beta1, fully promotes the early phase of the chondrogenic response by inducing cellular condensation followed by cartilage nodule formation in a mouse chondrogenic cell line, ATDC5. We investigated which, if any, of the three major types of MAP kinase plays a functional role in the promotion of chondrogenesis induced by **GDF-5**. **GDF-5** induced phosphorylation of p38 MAP kinase and extracellular signal-regulated kinase (ERK) but not that of c-Jun N-terminal kinase (JNK). The phosphorylation of p38 MAP kinase was also induced by **BMP**-2 and TGF-beta1. An inhibitor of p38 and p38 beta MAP kinase, SB202190, showed complete inhibition of cartilage nodule formation but failed to affect alkaline phosphatase (ALP) activity induced by **GDF-5**. Expression of the type II collagen gene, a hallmark of chondrogenesis in vertebrates, was also induced by **GDF -5** treatment and strongly suppressed by SB202190. On the other hand, although an inhibitor of MAP/ERK kinase, PD98059, inhibited the rapid phosphorylation of ERK by **GDF-5**, it inhibited neither ALP activity nor cartilage nodule formation induced by **GDF -5**. These results strongly suggest that the p38 MAP kinase cascade is involved in **GDF-5** signaling pathways and that a role of the p38 MAP kinase pathway is necessary over a longer period to promote chondrogenesis in ATDC5 cells.

L6 ANSWER 8 OF 17 MEDLINE DUPLICATE 4

1999134121 Document Number: 99134121. PubMed ID: 9950587. **Bone morphogenetic proteins** and growth and differentiation factors in the human cornea. You L; Kruse F E; Pohl J; Volcker H E. (Department of Ophthalmology, University of Heidelberg Medical School, Germany.) INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, (1999 Feb) 40 (2) 296-311. Journal code: GWI; 7703701. ISSN: 0146-0404. Pub. country: United States. Language: English.

AB PURPOSE: To investigate transcription of members of the transforming growth factor (**TGF**)-**beta** superfamily and corresponding receptors in human corneal epithelium and stroma. METHODS: Transcription of **bone morphogenetic proteins** (**BMP**)-2, **BMP**-3, **BMP**-4, **BMP**-5, and **BMP** -7; growth- differentiation factor (**GDF**)-**5**), and **BMP** receptors (BMPR) types I (BMPR-IA, BMPR-IB) and II (BMPR-II) was investigated by reverse transcription-polymerase chain reaction (RT-PCR) in ex vivo and cultured cells. For verification, PCR fragments were cloned and sequenced. DNA dot blot analysis was performed to estimate the level of transcription. RNA dot blots were performed to determine expression of **GDF-5**. Expression of **BMP** receptor proteins was investigated by immunohistochemistry. Single-cell clonal growth proliferation assays were performed using recombinant human **GDF-5** and TGF-beta1. RESULTS: Transcription of **BMP**-2, **BMP**-3, **BMP**-4, **BMP**-5, and **BMP**-7 and receptors of BMPR-IA, BMPR-IB and BMPR-II was detected in ex vivo and cultured epithelium and stroma. The level of transcription was higher in cultured stroma for all factors, but the level for the receptors was higher in cultured epithelium. In contrast **GDF-5** was transcribed only in stromal cells, suggesting that this cytokine may be an important mediator between keratocytes and epithelial cells. Furthermore, **GDF-5** inhibited proliferation of corneal epithelial and stromal cells. CONCLUSIONS: Given the importance of the **TGF-beta** family during embryonic development, the results suggest that its members may be components of the corneal cytokine network and may participate in the regulation of cellular proliferation

and differentiation.

L6 ANSWER 9 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1999:444197 Document No.: PREV199900444197. Cloning, expression profile, and genomic organization of the mouse STAP/A170 gene. Okazaki, Makoto; Ito, Sachiko; Kawakita, Koji; Takeshita, Sunao; Kawai, Shinji; Makishima, Fusao; Oda, Hiroaki (1); Kakinuma, Atsushi. (1) Laboratory of Nutritional Biochemistry, Division of Biochemistry, Department of Applied Molecular Biosciences, Nagoya University, Nagoya, 464-8601 Japan. Genomics, (Aug. 15, 1999) Vol. 60, No. 1, pp. 87-95. ISSN: 0888-7543. Language: English. Summary Language: English.

AB The preferential screening of cDNA libraries derived from the mouse osteoblastic cell line MC3T3-E1 has yielded a cDNA clone encoding a 442-amino-acid protein designated STAP (signal transduction and adaptor protein), which contains several motifs shared among transcription factors and adaptors such as a Zn-finger like motif, a proline-rich domain, and a PEST sequence. The amino acid sequence homology search also reveals that STAP is identical to a mouse oxidative stress protein, A170, and has 90% homology with a human p62 protein that binds to the tyrosine kinase p56lck SH2 domain. Northern blot analysis indicated a broad expression profile of STAP mRNA in various tissues and cell lines. In MC3T3-E1 cells, STAP mRNA was induced by treatment with **TGF-beta**, but not with **BMP**-2 or **GDF-5**. Analysis of the mouse STAP gene isolated from the genomic library revealed that the STAP gene spans a region of over 11 kb and comprises eight exons. The transcription start site was identified by primerextension analysis to be located 35 bp upstream from the translation initiation site. Sequencing analysis of the 5' flanking region of the STAP gene revealed multiple consensus motifs/sequences for several DNA binding transcription factors. The STAP gene had a TATA box, but no CCAAT box. Potential Sp1, AP-1, NF-E2, MyoD, and NF-kappaB binding sites were found in the 5' flanking region (1.4 kb) of the STAP gene.

L6 ANSWER 10 OF 17 SCISEARCH COPYRIGHT 2002 ISI (R)
1999:156022 The Genuine Article (R) Number: 167BX. Expression and function of **Gdf-5** during digit skeletogenesis in the embryonic chick leg bud. Merino R; Macias D; Ganan Y; Economides A N; Wang X; Wu Q; Stahl N; Sampath K T; Varona P; Hurle J M (Reprint). UNIV CANTABRIA, FAC MED, DEPT ANAT & CELLULAR BIOL, C CARDENAL HERRERA ORIA S-N, SANTANDER 39011, SPAIN (Reprint); UNIV CANTABRIA, FAC MED, DEPT ANAT & CELLULAR BIOL, SANTANDER 39011, SPAIN; UNIV EXTREMADURA, DEPT CIENCIAS MORFOL & BIOL ANIM & CELULAR, E-06071 BADAJOZ, SPAIN; REGENERON PHARMACEUT INC, TARRYTOWN, NY 10591; CREAT BIOMOL, HOPKINTON, MA 01748. DEVELOPMENTAL BIOLOGY (1 FEB 1999) Vol. 206, No. 1, pp. 33-45. Publisher: ACADEMIC PRESS INC. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0012-1606. Pub. country: SPAIN; USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Bone morphogenetic proteins** (**BMPs**) constitute a large family of secreted signals involved in the formation of the skeleton but the specific function of each member of this family remains elusive. **GDF-5** is a member of the **BMP** family which has been implicated in several skeletogenic events including the induction and growth of the appendicular cartilages, the determination of joint forming regions, and the establishment of tendons. Here, we have studied the function of **GDF-5** in digit skeletogenesis by analyzing the effects of its local administration in the developing autopod of embryonic chick and the regulation of its pattern of gene expression by other signals involved in digit morphogenesis. As reported in the mouse, the **gdf-5** gene exhibits a precise distribution in the joint-forming regions of the developing chicken digital rays. **GDF-5** beads implanted at the tip of the digits promote intense cartilage growth and fail to induce morphological or molecular signs of joint formation. Furthermore, **GDF-5** beads implanted in the interdigits inhibit the formation of joints in the adjacent digits. These data suggest that the role of

GDF-5 in joint formation is the control of growth and differentiation of the cartilage of the epiphyseal regions of the phalanges rather than accounting for the differentiation of the sinovial joint tissues. The interdigital mesoderm in spite of its potential to form ectopic digits with their tendinous apparatus failed to form either ectopic cartilages or ectopic tendons after the implantation of **GDF-5** beads in the stages preceding cell death. At difference with other **BMPs**, **GDF-5** exhibited only a weak cell death promoting effect. The **BMP** antagonist Noggin binds to **GDF-5** and is able to inhibit all the observed effects of this growth factor in vivo. Potential interactions of **GDF-5** with other signals involved in digits morphogenesis were also explored. **BMP**-7 regulates negatively the expression of **gdf-5** gene in the joint forming regions and local treatment with Noggin induces the ectopic expression of **gdf-5** in the interdigital mesoderm. Retroviral-induced misexpression of Indian or Sonic Hedgehog genes in the developing digits leads to the formation of digits without joints in which **gdf-5** expression occurs throughout the entire perichondrial surface. In conclusion, this study indicates that **GDF-5** is a signal regulated by other **BMPs** which controls the growth and differentiation of the epiphyses of the digital cartilages acting in close relationship with Hedgehog signaling. (C) 1999 Academic Press.

L6 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2002 ACS

1998:644096 Document No. 130:33401 Transforming growth factor-.beta. superfamily members expressed in rat incisor pulp. Nakashima, M.; Toyono, T.; Murakami, T.; Akamine, A. (Department of Operative Dentistry and Endodontology, Faculty of Dentistry, Kyushu University, Fukuoka, 812-82, Japan). Arch. Oral Biol., 43(9), 745-751 (English) 1998. CODEN: AOBIAR. ISSN: 0003-9969. Publisher: Elsevier Science Ltd..

AB The transforming growth factor (**TGF**)-.**beta**. superfamily comprises more than 35 structurally related genes that have been implicated in embryonic induction and morphogenesis. Different superfamily members may have distinct regulatory roles in tooth development and maintenance. Degenerate primer sets derived from the highly conserved carboxy terminal region of the **TGF**-.**beta**. superfamily were used for reverse transcriptase-polymerase with poly(A)+ RNA from the rat incisor pulp as a template. **TGF**-.**beta**. superfamily members expressed in the pulp with known potential to differentiate into odontoblasts and to form dentin were identified. Nucleotide-sequence anal. of the amplified cDNAs identified those encoding activin-.beta.B; bone morphogenic protein (**BMP**)-2, -4, -7 and -8; growth/differentiation factor (GDF)-1, -5 and -6; and glial cell line-derived neurotrophic factor. In addn., Northern blot anal. detected **TGF**-.**beta**.1, -.beta.2 and -.beta.3; activin-.beta.A; **BMP**-6 and GDF-7 mRNA transcripts in the pulp. Coordinated expression of **TGF**-.**beta**. superfamily members in pulp may be crit. in tooth development and repair.

L6 ANSWER 12 OF 17 SCISEARCH COPYRIGHT 2002 ISI (R)

1998:235848 The Genuine Article (R) Number: ZB929. Gene expression of growth and differentiation factors-5, -6, and -7 in developing bovine tooth at the root forming stage. Morotome Y (Reprint); GosekiSone M; Ishikawa I; Oida S. TOKYO MED & DENT UNIV, FAC DENT, DEPT PERIODONTOL, BUNKYO KU, 1-5-45 YUSHIMA, TOKYO 1138549, JAPAN (Reprint); TOKYO MED & DENT UNIV, FAC DENT, DEPT BIOCHEM, BUNKYO KU, TOKYO 1138549, JAPAN. BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS (6 MAR 1998) Vol. 244, No. 1, pp. 85-90. Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0006-291X. Pub. country: JAPAN. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Growth and differentiation factors (**GDF**)-**5**, -6, and -7 are members of the **bone morphogenetic protein** (**BMP**) family. Previous studies suggest their

importance in bone development and in tendon/ligament morphogenesis. The cells of the dental attachment apparatus, cementum, periodontal ligament, and alveolar bone proper are derived from the dental follicle proper. In this study, we investigated the expression of **GDF**-**5**, -6, and -7 genes in tissues of the bovine incisor tooth germ at the root forming stage. The results demonstrate distinct expression of GDFs in both the dental follicle and the odontoblast layer. While **GDF**-**5** and -6 mRNAs were expressed in both the dental follicle and the odontoblast layer, GDF-7 mRNA expression was detected only in the dental follicle. These results indicate that GDFs, expressed in the bovine tooth germ including the dental follicle, may be potent regulatory molecules in the development of the dental attachment apparatus. (C) 1998 Academic Press.

L6 ANSWER 13 OF 17 SCISEARCH COPYRIGHT 2002 ISI (R)

97:701312 The Genuine Article (R) Number: XV968. Growth/differentiation factor-5 induces angiogenesis in vivo. Yamashita H (Reprint); Shimizu A; Kato M; Nishitoh H; Ichijo H; Hanyu A; Morita I; Kimura M; Makishima F; Miyazono K. JAPANESE FDN CANC RES, INST CANC, DEPT BIOCHEM, TOSHIMA KU, 1-37-1 KAMI IKEBUKURO, TOKYO 170, JAPAN (Reprint); UNIV TOKYO, FAC MED, DEPT OPHTHALMOL, BUNKYO KU, TOKYO 113, JAPAN; TOKYO MED & DENT UNIV, GRAD SCH, DEPT PHYSIOL CHEM, BUNKYO KU, TOKYO 113, JAPAN; NIPPON HOECHST MARION ROUSSEL LTD, DIV RES & DEV, DISCOVERY RES LABS, KAWAGOE, SAITAMA 35011, JAPAN. EXPERIMENTAL CELL RESEARCH (25 AUG 1997) Vol. 235, No. 1, pp. 218-226. Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0014-4827. Pub. country: JAPAN. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Bone morphogenetic proteins** (**BMPs**) are multifunctional cytokines, which induce bone and cartilage formation and exert various other effects on many tissues, Since angiogenesis is involved in the bone formation process, certain members in the **BMP** family may induce angiogenesis. We examined the in vivo angiogenic activity of **BMP** family members, i.e., growth/differentiation factor (**GDF**)-**5** and **BMP**-2, **GDF**-**5** induced angiogenesis in both chick chorioallantoic membrane and rabbit cornea assays. In contrast **BMP**-2 did not induce angiogenesis. In order to elucidate the mechanism of angiogenesis, we examined the effects of **GDF**-**5** on cultured bovine aortic endothelial cells (BECs). **GDF**-**5** induced plasminogen activator activity and accelerated the migration of BECs in a chemotactic fashion, which may contribute to the process of angiogenesis in vivo. These results suggest that **GDF**-**5** is one of the molecules which induce angiogenesis in the bone formation process. (C) 1997 Academic Press.

L6 ANSWER 14 OF 17 MEDLINE DUPLICATE 5

97270847 Document Number: 97270847. PubMed ID: 9125848. Identification of receptors for **bone morphogenetic proteins**.

Nishitoh H. (Second Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Tokyo Medical and Dental University.) KOKUBYO GAKKAI ZASSHI. THE JOURNAL OF THE STOMATOLOGICAL SOCIETY, JAPAN, (1997 Mar) 64 (1) 24-37. Journal code: IQF; 0413677. ISSN: 0300-9149. Pub. country: Japan. Language: Japanese.

AB **Bone morphogenetic protein** (**BMP**)-7/osteogenic protein (OP)-1 and growth/differentiation factor (**GDF**)-**5** are members of the **BMP** family. **BMPs** transduce their effects through binding to two different types of serine/threonine kinase receptors, type I and type II. Here we investigated the binding and signaling properties of **BMP**-7/OP-1 and **GDF**-**5** through type I and type II receptors. **BMP**-7/OP-1 was found to bind Activin receptor-like kinase (ALK)-1 as well as ALK-3/BMPR-IA in ATDC5 cells. When ALK-1 or ALK-3/BMPR-IA was stably transfected into mink lung epithelial cells, ALK-1 and ALK-3/BMPR-IA mediated signals for **BMP**-7/OP-1 with heterogeneous

signaling specificities. **GDF-5** bound to ALK-6/BMPR-IB and **BMP** type II receptor (BMPR-II) but not to ALK-3/BMPR-IA in ROB-C26 cells. Analysis using COS-1 cells revealed that **GDF-5** bound to ALK-6/BMPR-IB, but not to the other type I receptors when expressed alone. When COS-1 cells were transfected with type II receptor cDNAs, **GDF-5** bound to Activin type II receptor (ActR-II) and type IIB receptors as well as BMPR-II but not to **TGF-beta** type II receptor. In the presence of type II receptors, **GDF-5** bound to different sets of type I receptors, but the binding was most efficient to ALK-6/BMPR-IB compared to the other type I receptors. Moreover, **GDF-5** transduced the signal efficiently by ALK-6/BMPR-IB in the presence of BMPR-II or ActR-II.

L6 ANSWER 15 OF 17 SCISEARCH COPYRIGHT 2002 ISI (R)
96:641971 The Genuine Article (R) Number: VE477. IDENTIFICATION OF TYPE-I AND TYPE-II SERINE/THREONINE KINASE RECEPTORS FOR GROWTH/DIFFERENTIATION FACTOR-5. NISHITOH H; ICHIJO H (Reprint); KIMURA M; MATSUMOTO T; MAKISHIMA F; YAMAGUCHI A; YAMASHITA H; ENOMOTO S; MIYAZONO K. JAPANESE FDN CANC RES, INST CANC, DEPT BIOCHEM, TOSHIMA KU, 1-37-1 KAMI IKEBUKURO, TOKYO 170, JAPAN (Reprint); JAPANESE FDN CANC RES, INST CANC, DEPT BIOCHEM, TOSHIMA KU, TOKYO 170, JAPAN; TOKYO MED & DENT UNIV, DEPT ORAL & MAXILLOFACIAL SURG 2, BUNKYO KU, TOKYO 113, JAPAN; HOECHST JAPAN LTD, DRUG DISCOVERY RES LABS, PHARMA RES & DEV DIV, KAWAGOE, SAITAMA 35011, JAPAN; SHOWA UNIV, SCH DENT, DEPT ORAL PATHOL, SHINAGAWA KU, TOKYO 142, JAPAN; UNIV TOKYO, FAC MED, DEPT OPHTHALMOL, BUNKYO KU, TOKYO 113, JAPAN. JOURNAL OF BIOLOGICAL CHEMISTRY (30 AUG 1996) Vol. 271, No. 35, pp. 21345-21352. ISSN: 0021-9258. Pub. country: JAPAN. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Growth/differentiation factor-5 (**GDF-5**) is a member of the **bone morphogenetic protein** (**BMP**) family, which plays an important role in bone development in vivo. Mutations in the **GDF-5** gene result in brachypodism in mice and Hunter-Thompson type chondrodysplasia in human. **BMPs** transduce their effects through binding to two different types of serine/threonine kinase receptors, type I and type II. However, binding abilities appear to be different among the members of the **BMP** family. **BMP**-4 binds to two different type I receptors, **BMP** receptors type IA (BMPR-IA) and type IB (BMPR-IB), and a type II receptor, **BMP** receptor type II (BMPR-II). In addition to these receptors, osteogenic protein-1 (OP-1, also known as **BMP**-7) binds to activin type I receptor (ActR-I) as well as activin type II receptors (ActR-II and ActR-IIB). Here we investigate the binding and signaling properties of **GDF-5** through type I and type II receptors. **GDF-5** induced alkaline phosphatase activity in a rat osteoprogenitor-like cell line, ROB-C26. I-125-**GDF-5** bound to BMPR-IB and BMPR-II but not to BMPR-IA in ROB-C26 cells and other nontransfected cell lines. Analysis using COS-1 cells transfected with the receptor cDNAs revealed that **GDF-5** bound to BMPR-IB but not to the other type I receptors when expressed alone. When COS-1 cells were transfected with type II receptor cDNAs, **GDF-5** bound to ActR-II, ActR-IIB, and BMPR-II but not to transforming growth factor-beta type II receptor, In the presence of type II receptors, **GDF-5** bound to different sets of type I receptors, but the binding was most efficient to BMPR-IB compared with the other type I receptors. Moreover, a transcriptional activation signal was efficiently transduced by BMPR-IB in the presence of BMPR-II or ActR-II after stimulation by **GDF-5**. These results suggest that BMPR-IB mediates certain signals for **GDF-5** after forming the heteromeric complex with BMPR-II or ActR-II.

L6 ANSWER 16 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
95175438 EMBASE Document No.: 1995175438. Functional analysis of mammalian members of the transforming growth factor-.beta. superfamily. Matzuk M.M..

Department of Pathology, Baylor College of Medicine,Houston, TX 77030, United States. Trends in Endocrinology and Metabolism 6/4 (120-127) 1995.
ISSN: 1043-2760. CODEN: TENME4. Pub. Country: United States. Language: English. Summary Language: English.

AB Analysis of growth factor function has come from studies both in vitro and in vivo. However, the generation of mice deficient in a specific growth factor via gene targeting (for example, 'knockout') strategies in embryonic stem (ES) cells will often evaluate the essential roles of the protein in vivo and, in many cases, discover new functions. In this review, studies to date are discussed on the generation and analysis of mice deficient in members of the transforming growth factor (**TGF -.beta.**) superfamily. Among the genes targeted via ES cell strategies are the **TGF-.beta.**1, Mullerian-inhibiting substance (MIS), inhibin .alpha., activin .beta.A, and activin .beta.B genes. In addition, the mouse short ear and brachypodism mutants and insertional mutant 413-d have been identified as mutations in the **BMP**-5, **GDF-5**, and nodal loci, respectively.
These studies have led to critical insights into the functions of these gene products and have further emphasized the importance of members of the **TGF-.beta.** superfamily in mammalian development, reproduction, and oncogenesis.

L6 ANSWER 17 OF 17 MEDLINE DUPLICATE 6
94195427 Document Number: 94195427. PubMed ID: 8145850. Limb alterations in brachypodism mice due to mutations in a new member of the **TGF beta**-superfamily. Storm E E; Huynh T V; Copeland N G; Jenkins N A; Kingsley D M; Lee S J. (Department of Developmental Biology, Beckman Center, Stanford University School of Medicine, California 94305-5427.)
NATURE, (1994 Apr 14) 368 (6472) 639-43. Journal code: NSC; 0410462.
ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The mutation brachypodism (bp) alters the length and number of bones in the limbs of mice but spares the axial skeleton. It illustrates the importance of specific genes in controlling the morphogenesis of individual skeletal elements in the tetrapod limb. We now report the isolation of three new members of the transforming growth factor-beta (**TGF-beta**) superfamily (growth/differentiation factors (**GDF**) **5**,6 and 7) and show by mapping, expression patterns and sequencing that mutations in Gdf5 are responsible for skeletal alterations in bp mice. GDF5 and the closely related GDF6 and GDF7 define a new subgroup of factors related to known bone- and cartilage-inducing molecules, the **bone morphogenetic proteins** (**BMPs**). Studies of Bmp5 mutations in short ear mice have shown that at least one other **BMP** gene is also required for normal skeletal development. The highly specific skeletal alterations in bp and short ear mice suggest that different members of the **BMP** family control the formation of different morphological features in the mammalian skeleton.

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(FILE 'HOME' ENTERED AT 19:28:44 ON 26 MAR 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 19:29:10 ON 26 MAR 2002

L1 78909 S TGF BETA
L2 3177 S L1 AND BONE MORPHOGENETIC PROTEIN
L3 2334 S L2 AND BMP
L4 0 S L3 AND "MP52"
L5 34 S L3 AND "GDF-5"
L6 17 DUP REMOVE L5 (17 DUPLICATES REMOVED)

=> s l3 and substitution
L7 9 L3 AND SUBSTITUTION

=> dup remove l7
PROCESSING COMPLETED FOR L7
L8 5 DUP REMOVE L7 (4 DUPLICATES REMOVED)

=> d l8 1-5 cbib abs

L8 ANSWER 1 OF 5 MEDLINE DUPLICATE 1
2001271812 Document Number: 21221086. PubMed ID: 11320249. Mutation in **bone morphogenetic protein** receptor-IB is associated with increased ovulation rate in Booroola Merino ewes. Mulsant P; Lecerf F; Fabre S; Schibler L; Monget P; Lanneluc I; Pisselet C; Riquet J; Monniaux D; Callebaut I; Cribiu E; Thimonier J; Teyssier J; Bodin L; Cognie Y; Chitour N; Elsen J M. (Institut National de la Recherche Agronomique, Laboratoire de Genetique Cellulaire, BP, 27, 31326 Castanet-Tolosan, France.. mulsant@toulouse.inra.fr) . PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2001 Apr 24) 98 (9) 5104-9. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Ewes from the Booroola strain of Australian Merino sheep are characterized by high ovulation rate and litter size. This phenotype is due to the action of the FecB(B) allele of a major gene named FecB, as determined by statistical analysis of phenotypic data. By genetic analysis of 31 informative half-sib families from heterozygous sires, we showed that the FecB locus is situated in the region of ovine chromosome 6 corresponding to the human chromosome 4q22-23 that contains the **bone morphogenetic protein** receptor IB (BMPR-IB) gene encoding a member of the transforming growth factor-beta (**TGF-beta**) receptor family. A nonconservative **substitution** (Q249R) in the BMPR-IB coding sequence was found to be associated fully with the hyperprolificacy phenotype of Booroola ewes. In vitro, ovarian granulosa cells from FecB(B)/FecB(B) ewes were less responsive than granulosa cells from FecB(+)/FecB(+) ewes to the inhibitory effect on steroidogenesis of GDF-5 and **BMP**-4, natural ligands of BMPR-IB. It is suggested that in FecB(B)/FecB(B) ewes, BMPR-IB would be inactivated partially, leading to an advanced differentiation of granulosa cells and an advanced maturation of ovulatory follicles.

L8 ANSWER 2 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001165446 EMBASE Estrogen modulates estrogen receptor .alpha. and .beta. expression, osteogenic activity, and apoptosis in mesenchymal stem cells (MSCs) of osteoporotic mice. Zhou S.; Zilberman Y.; Wassermann K.; Bain S.D.; Sadovsky Y.; Gazit D.. Dr. D. Gazit, Molecular Pathology Lab, Hebrew University-Hadassah Medical, Gene Therapy Center, P.O.B. 12272, Jerusalem 91120, Israel. dgaz@cc.huji.ac.il. Journal of Cellular Biochemistry 81/SUPPL. 36 (144-155) 2001.
Refs: 85.
ISSN: 0730-2312. CODEN: JCEBD5. Pub. Country: United States. Language: English. Summary Language: English.

AB In the mouse, ovariectomy (OVX) leads to significant reductions in cancellous bone volume while estrogen (17.beta.-estradiol, E2) replacement not only prevents bone loss but can increase bone formation. As the E2dependent increase in bone formation would require the proliferation and differentiation of osteoblast precursors, we hypothesized that E2 regulates mesenchymal stem cells (MSCs) activity in mouse bone marrow. We therefore investigated proliferation, differentiation, apoptosis, and estrogen receptor (ER) .alpha. and .beta. expression of primary culture MSCs isolated from OVX and sham-operated mice. MSCs, treated in vitro with 10(-7) M E2, displayed a significant increase in ER.alpha. mRNA and protein expression as well as alkaline phosphatase (ALP) activity and proliferation rate. In contrast, E2 treatment resulted in a decrease in ER.beta. mRNA and protein expression as well as apoptosis in both OVX and sham mice. E2 up-regulated the mRNA expression of osteogenic genes for ALP, collagen I, **TGF-.beta**.1, **BMP**-2, and cbfa1 in MSCs. In a comparison of the relative mRNA expression and protein

levels for two ER isoforms, ER.alpha. was the predominant form expressed in MSCs obtained from both OVX and sham-operated mice. Cumulatively, these results indicate that estrogen in vitro directly augments the proliferation and differentiation, ER.alpha. expression, osteogenic gene expression and, inhibits apoptosis and ER.beta. expression in MSCs obtained from OVX and sham-operated mice. Co-expression of ER.alpha., but not ER.beta., and osteogenic differentiation markers might indicate that ER.alpha. function as an activator and ER.beta. function as a repressor in the osteogenic differentiation in MSCs. These results suggest that mouse MSCs are anabolic targets of estrogen action, via ERc.alpha. activation. .COPYRGT. Wiley-Liss, Inc.

L8 ANSWER 3 OF 5 MEDLINE

2000471997 Document Number: 20341087. PubMed ID: 10880444. **BMP**-2 antagonists emerge from alterations in the low-affinity binding epitope for receptor BMPR-II. Kirsch T; Nickel J; Sebald W. (Lehrstuhl fur Physiologische Chemie II, Theodor-Boveri-Institut fur Biowissenschaften (Biozentrum) der Universitat Wurzburg, Am Hubland, 97074 Wurzburg, Germany.) EMBO JOURNAL, (2000 Jul 3) 19 (13) 3314-24. Journal code: EMB; 8208664. ISSN: 0261-4189. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Bone morphogenetic protein**-2 (**BMP**-2) induces bone formation and regeneration in adult vertebrates and regulates important developmental processes in all animals. **BMP**-2 is a homodimeric cysteine knot protein that, as a member of the transforming growth factor-beta (**TGF-beta**) superfamily, signals by oligomerizing type I and type II receptor serine-kinases in the cell membrane. The binding epitopes of **BMP**-2 for BMPR-IA (type I) and BMPR-II or ActR-II (type II) were characterized using **BMP**-2 mutant proteins for analysis of interactions with receptor ectodomains. A large epitope 1 for high-affinity BMPR-IA binding was detected spanning the interface of the **BMP**-2 dimer. A smaller epitope 2 for the low-affinity binding of BMPR-II was found to be assembled by determinants of a single monomer. Symmetry-related pairs of the two juxtaposed epitopes occur near the **BMP**-2 poles. Mutations in both epitopes yielded variants with reduced biological activity in C2C12 cells; however, only epitope 2 variants behaved as antagonists partially or completely inhibiting **BMP**-2 activity. These findings provide a framework for the molecular description of receptor recognition and activation in the **BMP/TGF-beta** superfamily.

L8 ANSWER 4 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2000204007 EMBASE New factors controlling bone remodeling. Marie P.; Debiais F.; Cohen-Solal M.; De Vernejoul M.C.. P. Marie, INSERM U349, Viggo Petersen Center, Lariboisiere Teaching Hospital, 2, rue Ambroise-Pare, 75475 Paris, France. Joint Bone Spine 67/3 (150-156) 2000.
Refs: 66.
ISSN: 1169-8446. CODEN: JBSPFA. Pub. Country: France. Language: English. Summary Language: English.

AB Two factors of crucial importance in bone cell differentiation were discovered within the last two years. One is the transcription factor Osf2/Cbfa1, which allows mesenchymal stem cells to differentiate into osteoblasts. Soluble factors, including **bone morphogenetic proteins** (**BMPs**), leptin, and **TGF-.beta.**, can modulate differentiation of mesenchymal stem cells to osteoblasts or to other cell types such as chondrocytes or adipocytes. The other recent discovery is osteoclast differentiating factor (ODF), which is specific for and indispensable to osteoclast differentiation. ODF belongs to the TNF family. Its soluble receptor, osteoprotegerin, prevents it from binding to osteoclasts, thus inhibiting its activity. A role of lymphocytes in bone remodeling has long been suspected, and it has now been shown that ODF is produced by activated T lymphocytes, which may therefore be implicated in bone loss accompanying inflammation. Finally, recent evidence supports a role for B lymphocytes

in bone loss secondary to estrogen deprivation. In conclusion, these recent data may have important applications. Osteoprotegerin is a potent antiosteoclast agent that may prove useful in the treatment of bone disorders. Osf2/Cbfa1 and ODF are major targets in the treatment of osteoporosis. (C) 2000 Editions scientifiques et medicales Elsevier SAS.

L8 ANSWER 5 OF 5 MEDLINE
92246938 Document Number: 92246938. PubMed ID: 1575734. Evolutionary grouping of the transforming growth factor-beta superfamily. Burt D W. (Department of Cellular and Molecular Biology, AFRC Institute of Animal Physiology and Genetics Research, Roslin, Midlothian, UK.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1992 Apr 30) 184 (2) 590-5. Journal code: 9Y8; 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB **TGF beta** 1 is the prototype of a superfamily of differentiation factors with at least 18 distinct members. This classification is based on amino acid homology in the C-terminus of these polypeptides. The rates of amino acid **substitution** for several family members were estimated from a comparison of homologous sequences derived from different species. These rates were approximately constant for any given protein, but values varied greatly between different groups. This variation is a reflection of the great functional diversity found within the **TGF beta** superfamily. Maximum parsimony analysis allowed us to classify members of the **TGF beta** superfamily into five main groups (INH alpha, MIS, **TGF beta** s, INH beta s and **BMPs**) and various subgroups. This classification predicts possible phylogenetic relationships among these proteins. In the future, it is hoped that this method of classification will be adopted by all our colleagues, as an aid in deciding whether newly discovered proteins are the product of duplicated or homologous genes. This would suggest proteins with either similar or identical functions.

=> s l2 an monomer
MISSING OPERATOR L2 AN
The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

=> s l2 and monomer
L9 28 L2 AND MONOMER

=> s l9 and amino acid substitution
L10 1 L9 AND AMINO ACID SUBSTITUTION

=> d l10 cbib abs

L10 ANSWER 1 OF 1 MEDLINE
2000471997 Document Number: 20341087. PubMed ID: 10880444. BMP-2 antagonists emerge from alterations in the low-affinity binding epitope for receptor BMPR-II. Kirsch T; Nickel J; Sebald W. (Lehrstuhl fur Physiologische Chemie II, Theodor-Boveri-Institut fur Biowissenschaften (Biozentrum) der Universitat Wurzburg, Am Hubland, 97074 Wurzburg, Germany.) EMBO JOURNAL, (2000 Jul 3) 19 (13) 3314-24. Journal code: EMB; 8208664. ISSN: 0261-4189. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Bone morphogenetic protein**-2 (BMP-2) induces bone formation and regeneration in adult vertebrates and regulates important developmental processes in all animals. BMP-2 is a homodimeric cysteine knot protein that, as a member of the transforming growth factor-beta (**TGF-beta**) superfamily, signals by oligomerizing type I and type II receptor serine-kinases in the cell membrane. The binding epitopes of BMP-2 for BMPR-IA (type I) and BMPR-II or ActR-II (type II) were characterized using BMP-2 mutant proteins for analysis of interactions with receptor ectodomains. A large epitope 1 for high-affinity BMPR-IA binding was detected spanning the interface of the

BMP-2 dimer. A smaller epitope 2 for the low-affinity binding of BMPR-II was found to be assembled by determinants of a single **monomer**. Symmetry-related pairs of the two juxtaposed epitopes occur near the BMP-2 poles. Mutations in both epitopes yielded variants with reduced biological activity in C2C12 cells; however, only epitope 2 variants behaved as antagonists partially or completely inhibiting BMP-2 activity. These findings provide a framework for the molecular description of receptor recognition and activation in the BMP/**TGF-beta** superfamily.

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=> s BMP substitution
L11          0 BMP SUBSTITUTION

=> s BMP
L12      13924 BMP

=> s l12 and cysteine
L13        199 L12 AND CYSTEINE

=> s l13 and replacement
L14          1 L13 AND REPLACEMENT

=> d l14 cbib abs

L14  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
1998:485186   Document No. 129:108081  Process for preparing purified dimer of
     bone-morphogenic protein (BMP). Honda, Jun; Andou, Hidetoshi;
     Sugimoto, Shunjiro (Hoechst Marion Roussel Ltd., Japan). PCT Int. Appl.
     WO 9829559 A1 19980709, 15 pp. DESIGNATED STATES: W: AL, AU, BA, BB, BG,
     BR, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV,
     MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN,
     YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH,
     CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL,
     PT, SE, SN, TD, TG.  (Japanese). CODEN: PIXXD2. APPLICATION: WO
     1997-JP4784 19971224.  PRIORITY: JP 1996-355812 19961225.
AB   A process for prepg. a purified dimer of a bone-derived protein, which
     comprises subjecting an inclusion body of a BMP produced by
     genetic engineering to the following steps in sequence: incubation of an
     inclusion body of a BMP with an unfolding agent to prep. a
     solubilized monomer; again inclusion of the solubilized monomer with a
     refolding soln. to prep. a dimer; subjecting the refolded dimer to
     ultrafiltration and solvent replacement; subjecting the
     resultant dimer soln. to isoelec. pptn.; and subjecting the isoelec. pptd.
     dimer to reversed phase chromatog.  The method is useful for com. manuf.
     of purified dimer of BMP.


=> s l4 and serine
L15          0 L4 AND SERINE

=> s l4 and threonine
L16          0 L4 AND THREONINE

=> d his

     (FILE 'HOME' ENTERED AT 19:28:44 ON 26 MAR 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 19:29:10 ON
     26 MAR 2002
L1         78909 S TGF BETA
L2          3177 S L1 AND BONE MORPHOGENETIC PROTEIN
L3          2334 S L2 AND BMP
L4             0 S L3 AND "MP52"
L5            34 S L3 AND "GDF-5"
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L6            17 DUP REMOVE L5 (17 DUPLICATES REMOVED)
L7             9 S L3 AND SUBSTITUTION
L8             5 DUP REMOVE L7 (4 DUPLICATES REMOVED)
L9            28 S L2 AND MONOMER
L10            1 S L9 AND AMINO ACID SUBSTITUTION
L11            0 S BMP SUBSTITUTION
L12        13924 S BMP
L13          199 S L12 AND CYSTEINE
L14            1 S L13 AND REPLACEMENT
L15            0 S L4 AND SERINE
L16            0 S L4 AND THREONINE

=> s l13 and serine
L17           27 L13 AND SERINE

=> s l17 and threonine
L18           13 L17 AND THREONINE

=> s l18 and alanine
L19            1 L18 AND ALANINE

=> d l19 cbib abs

L19  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
1997:519474   Document No. 127:194854  Effect of ultrasonic and alkaline
     pretreatment on waste activated sludge characterization.  Chiu, Ying-Chih;
     Chang, Cheng-Nan; Huang, Wei-Shiang; Chao, Allen C. (Department of
     Environmental Engineering, National I-Lan Institute of Agriculture and
     Technology, I-Lan, Taiwan).  Zhongguo Huanjing Gongcheng Xuekan, 7(1),
     25-33 (English) 1997.  CODEN: ZHGXEL.  ISSN: 1022-7636.  Publisher:
     Chinese Institute of Environmental Engineering.
AB   Pretreatment of waste activated sludge results in an improved efficiency
     of the subsequent biol. anaerobic digestion process.  The pretreatment
     process has been carried out using alk. or ultrasonic treatment.
     Ultrasonic treatment followed by alk. treatment was more effective in
     dissolving org. N and carbohydrates than either ultrasonic or alk.
     treatment.  The improved efficiency was evaluated on the quantity of sol.
     substances and the av. mol. wt. of the treated waste activated sludge as
     well as by the biol. methane potential (BMP) test.  With
     ultrasonic treatment for 10.8 s/mL followed by treatment with 40 meq/L
     NaOH for 24 h, the ratio of sol. COD (SCOD) to total COD (TCOD) of the
     treated sludge increased from 2 to 81%, the av. mol. wt. was reduced from
     31,000 to 8500 amu, and the total concn. of amino acids was significantly
     raised from 1.8 to 167.8 mg-N/L.  Results of the 24-day BMP test
     showed that TCOD removal of the treated sludge increased from 35 to 51%
     and that methane prodn. was improved from 0.33 to 0.37 m3-CH4/kg-COD.


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     (FILE 'HOME' ENTERED AT 19:28:44 ON 26 MAR 2002)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 19:29:10 ON
     26 MAR 2002
L1         78909 S TGF BETA
L2          3177 S L1 AND BONE MORPHOGENETIC PROTEIN
L3          2334 S L2 AND BMP
L4             0 S L3 AND "MP52"
L5            34 S L3 AND "GDF-5"
L6            17 DUP REMOVE L5 (17 DUPLICATES REMOVED)
L7             9 S L3 AND SUBSTITUTION
L8             5 DUP REMOVE L7 (4 DUPLICATES REMOVED)
L9            28 S L2 AND MONOMER
L10            1 S L9 AND AMINO ACID SUBSTITUTION
L11            0 S BMP SUBSTITUTION
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L12        13924 S BMP
L13          199 S L12 AND CYSTEINE
L14            1 S L13 AND REPLACEMENT
L15            0 S L4 AND SERINE
L16            0 S L4 AND THREONINE
L17           27 S L13 AND SERINE
L18           13 S L17 AND THREONINE
L19            1 S L18 AND ALANINE

=> dup remove l16
L16 HAS NO ANSWERS

=> dup remove l17
PROCESSING COMPLETED FOR L17
L20            7 DUP REMOVE L17 (20 DUPLICATES REMOVED)

=> d l20 1-7 cbib abs

L20  ANSWER 1 OF 7     MEDLINE                              DUPLICATE 1
2001226905  Document Number: 21124975.    PubMed ID: 11222140.   The type I
     serine/threonine kinase receptor Alk8/Lost-a-fin is required for
     Bmp2b/7 signal transduction during dorsoventral patterning of the
     zebrafish embryo. Bauer H; Lele Z; Rauch G J; Geisler R; Hammerschmidt M.
     (Hans-Spemann Laboratory, Max-Planck Institut fur Immunbiologie, Stuebeweg
     51, D-79108 Freiburg, Germany. ) DEVELOPMENT, (2001 Mar) 128 (6) 849-58.
     Journal code: ECW; 8701744. ISSN: 0950-1991. Pub. country: England: United
     Kingdom. Language: English.
AB   Ventral specification of mesoderm and ectoderm depends on signaling by
     members of the bone morphogenetic protein (Bmp) family.
     Bmp signals are transmitted by a complex of type I and type II
     serine/threonine kinase transmembrane receptors. Here, we show
     that Alk8, a novel member of the Alk1 subgroup of type I receptors, is
     disrupted in zebrafish lost-a-fin (laf) mutants. Two alk8/laf null alleles
     are described. In laf(tm110), a conserved extracellular cysteine
     residue is replaced by an arginine, while in laf(m100), Alk8 is
     prematurely terminated directly after the transmembrane domain. The
     zygotic effect of both mutations leads to dorsalization of intermediate
     strength. A much stronger dorsalization, similar to that of bmp2b/swirl
     and bmp7/snailhouse mutants, however, is obtained by inhibiting both
     maternally and zygotically supplied alk8 gene products with morpholino
     antisense oligonucleotides. The phenotype of laf mutants and alk8
     morphants can be rescued by injected mRNA encoding Alk8 or the Bmp
     -regulated transcription factor Smad5, but not by mRNA encoding Bmp2b or
     Bmp7. Conversely, injected mRNA encoding a constitutively active version
     of Alk8 can rescue the strong dorsalization of bmp2b/swirl and
     bmp7/snailhouse mutants, whereas smad5/somitabun mutant embryos do not
     respond. Altogether, the data suggest that Alk8 acts as a Bmp2b/7 receptor
     upstream of Smad5.

L20  ANSWER 2 OF 7     MEDLINE                              DUPLICATE 2
2001314104  Document Number: 21280915.    PubMed ID: 11386757.   Central
     nervous system, uterus, heart, and leukocyte expression of the LOXL3 gene,
     encoding a novel lysyl oxidase-like protein. Jourdan-Le Saux C; Tomsche A;
     Ujfalusi A; Jia L; Csiszar K. (Pacific Biomedical Research Center,
     University of Hawaii, 1993 East-West Road, Honolulu, Hawaii, 96822. )
     GENOMICS, (2001 Jun 1) 74 (2) 211-8. Journal code: GEN; 8800135. ISSN:
     0888-7543. Pub. country: United States. Language: English.
AB   A BLASTN search using the mouse lor-2 cDNA identified three overlapping
     ESTs (AI752772, AA852888, and R55706) in the GenBank database. These
     expressed sequence tags were assembled into a contig of 3121 nucleotides
     with an open reading frame of 2262 bp. The encoded putative polypeptide of
     754 amino acids presented all structural characteristics of the lysyl
     oxidase (LOX) enzyme family, a copper-binding site with four histidyl
     residues, the lysyl and tyrosyl residues known to be involved in LOX
     enzyme in the formation of the quinone cofactor and surrounding sequences,
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and the cytokine receptor-like domain. In addition, four scavenger receptor **cysteine**-rich (SRCR) domains were found in the N-terminal region of the protein. The gene encoding this new cDNA, which we have referred to as human lysyl oxidase-like 3 (humanLOXL3), has been mapped to chromosome 2p13.3, overlapping at its 3' end the HtrA2 **serine** protease gene. The structure of the humanLOXL3 gene was deduced from the BAC clone bac91a19 sequence and contained 14 exons. The expression pattern of this new member of the LOX gene family appears to be different from that of the LOX and LOX-like genes, as the central nervous system, neurons, and also leukocytes expressed humanLOXL3. A BLASTN search of the human EST database indicated the presence of ESTs, corresponding to alternative splice variants of LOXL3, that lacked exon 5 and exon 8. The putative resulting protein retained the region encoding the structural and functional elements of the amine oxidase but the second and fourth SRCR domains were truncated and the potential **BMP**-1 cleavage site was not present. The presence of domains unrelated to the traditional amine oxidase activity is a strong indication that humanLOXL3 might fulfill other functions in addition to intrinsic enzyme activity.

L20 ANSWER 3 OF 7 MEDLINE DUPLICATE 3
2000471997 Document Number: 20341087. PubMed ID: 10880444. **BMP**-2 antagonists emerge from alterations in the low-affinity binding epitope for receptor BMPR-II. Kirsch T; Nickel J; Sebald W. (Lehrstuhl fur Physiologische Chemie II, Theodor-Boveri-Institut fur Biowissenschaften (Biozentrum) der Universitat Wurzburg, Am Hubland, 97074 Wurzburg, Germany.) EMBO JOURNAL, (2000 Jul 3) 19 (13) 3314-24. Journal code: EMB; 8208664. ISSN: 0261-4189. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Bone morphogenetic protein-2 (**BMP**-2) induces bone formation and regeneration in adult vertebrates and regulates important developmental processes in all animals. **BMP**-2 is a homodimeric **cysteine** knot protein that, as a member of the transforming growth factor-beta (TGF-beta) superfamily, signals by oligomerizing type I and type II receptor **serine**-kinases in the cell membrane. The binding epitopes of **BMP**-2 for BMPR-IA (type I) and BMPR-II or ActR-II (type II) were characterized using **BMP**-2 mutant proteins for analysis of interactions with receptor ectodomains. A large epitope 1 for high-affinity BMPR-IA binding was detected spanning the interface of the **BMP**-2 dimer. A smaller epitope 2 for the low-affinity binding of BMPR-II was found to be assembled by determinants of a single monomer. Symmetry-related pairs of the two juxtaposed epitopes occur near the **BMP**-2 poles. Mutations in both epitopes yielded variants with reduced biological activity in C2C12 cells; however, only epitope 2 variants behaved as antagonists partially or completely inhibiting **BMP**-2 activity. These findings provide a framework for the molecular description of receptor recognition and activation in the **BMP**/TGF-beta superfamily.

L20 ANSWER 4 OF 7 CAPLUS
2000:336125 Document No. 133:87266 Differential gene expression by endothelial cells in distinct angiogenic states. Glienke, Jens; Schmitt, Armin O.; Pilarsky, Christian; Hinzmann, Bernd; Weiss, Bertram; Rosenthal, Andre; Thierauch, Karl-Heinz (Research Laboratories of Schering AG, Berlin, D-13342, Germany). European Journal of Biochemistry, 267(9), 2820-2830 (English) 2000. CODEN: EJBCAI. ISSN: 0014-2956. Publisher: Blackwell Science Ltd..

AB Angiogenesis is a complex process that can be regarded as a series of sequential events comprising a variety of tissue cells. The major problem when studying angiogenesis in vitro is the lack of a model system mimicking the various aspects of the process in vivo. In this study we have used two in vitro models, each representing different and distinct aspects of angiogenesis. Differentially expressed genes in the two culture forms were identified using the suppression subtractive hybridization technique to prep. subtracted cDNA libraries. This was

followed by a differential hybridization screen to pick up overexpressed clones. Using comparative multiplex RT-PCR we confirmed the differential expression and showed differences up to 14-fold. We identified a broad range of genes already known to play an important role during angiogenesis like Flt1 or TIE2. Furthermore several known genes are put into the context of endothelial cell differentiation, which up to now have not been described as being relevant to angiogenesis, like NrCAM, Claudin14, **BMP**-6, PEA-15 and PINCH. With ADAMTS4 and hADMTS1/METH-1 we further extended the set of matrix metalloproteases expressed and regulated by endothelial cells.

L20 ANSWER 5 OF 7 MEDLINE DUPLICATE 4
2000200132 Document Number: 20200132. PubMed ID: 10733942.
Characterization of the functionally related sites in the neural inducing gene noggin. Liu W; Ren C; Shi J; Feng X; He Z; Xu L; Lan K; Xie L; Peng Y; Fan J; Kung H f; Yao K T; Xu R H. (Cancer Research Institute, Hunan Medical University, Changsha, Hunan, 410078, China.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Apr 2) 270 (1) 293-7. Journal code: 9Y8; 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Previously we have shown that blocking bone morphogenetic protein (**BMP**) receptor signaling by a dominant negative **BMP** receptor causes neurogenesis in Xenopus animal caps (ACs), whereas the physiological neural inducer noggin acts as a homodimer physically binding to **BMP**-4 and disrupting its signaling at the ligand level. The present study attempted to elucidate the relationship between the structure and function of noggin. By replacing some **cysteine** residues with **serine** residues through a site-directed mutagenesis strategy, we generated three noggin mutants, C145S, C205S, and C(218, 220, 222)S (3CS). Although mRNAs encoded by these mutants were translated as efficiently as wild-type (WT) noggin mRNA, they behaved differently when expressed in vivo. Expression of WT noggin or C205S in Xenopus ACs converted the explants (prospective ectoderm) into neural tissue, indicated by the neural-like morphology and expression of the pan neural marker NCAM in the ACs. In contrast, ACs expressing C145S or 3CS sustained an epidermal fate like the control caps. Similar results were observed in the mesoderm where C205S (but not C145S and 3CS) displayed dorsalizing activity as well as WT noggin. Altogether, our results suggest that Cys145 alone or Cys(218, 220, 222) as a whole in noggin protein is required for the biological activities of noggin, probably participating in the dimerization of noggin with **BMP**-4 or itself.

L20 ANSWER 6 OF 7 CAPLUS
1997:519474 Document No. 127:194854 Effect of ultrasonic and alkaline pretreatment on waste activated sludge characterization. Chiu, Ying-Chih; Chang, Cheng-Nan; Huang, Wei-Shiang; Chao, Allen C. (Department of Environmental Engineering, National I-Lan Institute of Agriculture and Technology, I-Lan, Taiwan). Zhongguo Huanjing Gongcheng Xuekan, 7(1), 25-33 (English) 1997. CODEN: ZHGXEL. ISSN: 1022-7636. Publisher: Chinese Institute of Environmental Engineering.

AB Pretreatment of waste activated sludge results in an improved efficiency of the subsequent biol. anaerobic digestion process. The pretreatment process has been carried out using alk. or ultrasonic treatment. Ultrasonic treatment followed by alk. treatment was more effective in dissolving org. N and carbohydrates than either ultrasonic or alk. treatment. The improved efficiency was evaluated on the quantity of sol. substances and the av. mol. wt. of the treated waste activated sludge as well as by the biol. methane potential (**BMP**) test. With ultrasonic treatment for 10.8 s/mL followed by treatment with 40 meq/L NaOH for 24 h, the ratio of sol. COD (SCOD) to total COD (TCOD) of the treated sludge increased from 2 to 81%, the av. mol. wt. was reduced from 31,000 to 8500 amu, and the total concn. of amino acids was significantly raised from 1.8 to 167.8 mg-N/L. Results of the 24-day **BMP** test showed that TCOD removal of the treated sludge increased from 35 to 51%

and that methane prodn. was improved from 0.33 to 0.37 m3-CH4/kg-COD.

L20 ANSWER 7 OF 7 MEDLINE DUPLICATE 5
97114070 Document Number: 97114070. PubMed ID: 8955889. Identification and cloning of a novel type I **serine**/threonine kinase receptor of the TGF-beta/**BMP** superfamily in rat prostate. Kang Y; Reddi A H. (Department of Orthopaedic Surgery, Johns Hopkins Oncology Center, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.) BIOCHEMISTRY AND MOLECULAR BIOLOGY INTERNATIONAL, (1996 Nov) 40 (5) 993-1001. Journal code: BOD; 9306673. ISSN: 1039-9712. Pub. country: Australia. Language: English.

AB A cDNA clone encoding a new member of the type I **serine** /threonine kinase receptors of the TGF-beta/**BMP** superfamily was isolated from a rat prostate cDNA library. The predicted sequence of the encoded protein is 493 amino acids with a molecular weight of 55 kDa. It contains a putative **cysteine** rich extracellular domain, a transmembrane domain, a conserved type I receptor GS domain and a cytoplasmic **serine**/threonine kinase domain. The kinase domain shares 80% homology with that of ALK-4 and ALK-5 whose ligands are activin and TGF-beta. Northern blot analysis revealed that this prostate **serine**/threonine kinase receptor I (PSKR-I) is highly expressed in rat dorsolateral prostate, coagulating gland (anterior prostate), cerebellum and adipose tissue.

=> dup remove l18
PROCESSING COMPLETED FOR L18
L21 5 DUP REMOVE L18 (8 DUPLICATES REMOVED)

=> d l21 1-5 cbib abs

L21 ANSWER 1 OF 5 MEDLINE DUPLICATE 1
2001226905 Document Number: 21124975. PubMed ID: 11222140. The type I **serine/threonine** kinase receptor Alk8/Lost-a-fin is required for Bmp2b/7 signal transduction during dorsoventral patterning of the zebrafish embryo. Bauer H; Lele Z; Rauch G J; Geisler R; Hammerschmidt M. (Hans-Spemann Laboratory, Max-Planck Institut fur Immunbiologie, Stuebeweg 51, D-79108 Freiburg, Germany.) DEVELOPMENT, (2001 Mar) 128 (6) 849-58. Journal code: ECW; 8701744. ISSN: 0950-1991. Pub. country: England: United Kingdom. Language: English.

AB Ventral specification of mesoderm and ectoderm depends on signaling by members of the bone morphogenetic protein (**Bmp**) family. **Bmp** signals are transmitted by a complex of type I and type II **serine/threonine** kinase transmembrane receptors. Here, we show that Alk8, a novel member of the Alk1 subgroup of type I receptors, is disrupted in zebrafish lost-a-fin (laf) mutants. Two alk8/laf null alleles are described. In laf(tm110), a conserved extracellular **cysteine** residue is replaced by an arginine, while in laf(m100), Alk8 is prematurely terminated directly after the transmembrane domain. The zygotic effect of both mutations leads to dorsalization of intermediate strength. A much stronger dorsalization, similar to that of bmp2b/swirl and bmp7/snailhouse mutants, however, is obtained by inhibiting both maternally and zygotically supplied alk8 gene products with morpholino antisense oligonucleotides. The phenotype of laf mutants and alk8 morphants can be rescued by injected mRNA encoding Alk8 or the **Bmp**-regulated transcription factor Smad5, but not by mRNA encoding Bmp2b or Bmp7. Conversely, injected mRNA encoding a constitutively active version of Alk8 can rescue the strong dorsalization of bmp2b/swirl and bmp7/snailhouse mutants, whereas smad5/somitabun mutant embryos do not respond. Altogether, the data suggest that Alk8 acts as a Bmp2b/7 receptor upstream of Smad5.

L21 ANSWER 2 OF 5 MEDLINE
2000471997 Document Number: 20341087. PubMed ID: 10880444. **BMP** -2 antagonists emerge from alterations in the low-affinity binding epitope

for receptor BMPR-II. Kirsch T; Nickel J; Sebald W. (Lehrstuhl fur Physiologische Chemie II, Theodor-Boveri-Institut fur Biowissenschaften (Biozentrum) der Universitat Wurzburg, Am Hubland, 97074 Wurzburg, Germany.) EMBO JOURNAL, (2000 Jul 3) 19 (13) 3314-24. Journal code: EMB; 8208664. ISSN: 0261-4189. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Bone morphogenetic protein-2 (**BMP**-2) induces bone formation and regeneration in adult vertebrates and regulates important developmental processes in all animals. **BMP**-2 is a homodimeric **cysteine** knot protein that, as a member of the transforming growth factor-beta (TGF-beta) superfamily, signals by oligomerizing type I and type II receptor **serine**-kinases in the cell membrane. The binding epitopes of **BMP**-2 for BMPR-IA (type I) and BMPR-II or ActR-II (type II) were characterized using **BMP**-2 mutant proteins for analysis of interactions with receptor ectodomains. A large epitope 1 for high-affinity BMPR-IA binding was detected spanning the interface of the **BMP**-2 dimer. A smaller epitope 2 for the low-affinity binding of BMPR-II was found to be assembled by determinants of a single monomer. Symmetry-related pairs of the two juxtaposed epitopes occur near the **BMP**-2 poles. Mutations in both epitopes yielded variants with reduced biological activity in C2C12 cells; however, only epitope 2 variants behaved as antagonists partially or completely inhibiting **BMP**-2 activity. These findings provide a framework for the molecular description of receptor recognition and activation in the **BMP**/TGF-beta superfamily.

L21 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2002 ACS

2000:336125 Document No. 133:87266 Differential gene expression by endothelial cells in distinct angiogenic states. Glienke, Jens; Schmitt, Armin O.; Pilarsky, Christian; Hinzmann, Bernd; Weiss, Bertram; Rosenthal, Andre; Thierauch, Karl-Heinz (Research Laboratories of Schering AG, Berlin, D-13342, Germany). European Journal of Biochemistry, 267(9), 2820-2830 (English) 2000. CODEN: EJBCAI. ISSN: 0014-2956. Publisher: Blackwell Science Ltd..

AB Angiogenesis is a complex process that can be regarded as a series of sequential events comprising a variety of tissue cells. The major problem when studying angiogenesis in vitro is the lack of a model system mimicking the various aspects of the process in vivo. In this study we have used two in vitro models, each representing different and distinct aspects of angiogenesis. Differentially expressed genes in the two culture forms were identified using the suppression subtractive hybridization technique to prep. subtracted cDNA libraries. This was followed by a differential hybridization screen to pick up overexpressed clones. Using comparative multiplex RT-PCR we confirmed the differential expression and showed differences up to 14-fold. We identified a broad range of genes already known to play an important role during angiogenesis like Flt1 or TIE2. Furthermore several known genes are put into the context of endothelial cell differentiation, which up to now have not been described as being relevant to angiogenesis, like NrCAM, Claudin14, **BMP**-6, PEA-15 and PINCH. With ADAMTS4 and hADMTS1/METH-1 we further extended the set of matrix metalloproteases expressed and regulated by endothelial cells.

L21 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2002 ACS

1997:519474 Document No. 127:194854 Effect of ultrasonic and alkaline pretreatment on waste activated sludge characterization. Chiu, Ying-Chih; Chang, Cheng-Nan; Huang, Wei-Shiang; Chao, Allen C. (Department of Environmental Engineering, National I-Lan Institute of Agriculture and Technology, I-Lan, Taiwan). Zhongguo Huanjing Gongcheng Xuekan, 7(1), 25-33 (English) 1997. CODEN: ZHGXEL. ISSN: 1022-7636. Publisher: Chinese Institute of Environmental Engineering.

AB Pretreatment of waste activated sludge results in an improved efficiency of the subsequent biol. anaerobic digestion process. The pretreatment process has been carried out using alk. or ultrasonic treatment. Ultrasonic treatment followed by alk. treatment was more effective in

dissolving org. N and carbohydrates than either ultrasonic or alk. treatment. The improved efficiency was evaluated on the quantity of sol. substances and the av. mol. wt. of the treated waste activated sludge as well as by the biol. methane potential (**BMP**) test. With ultrasonic treatment for 10.8 s/mL followed by treatment with 40 meq/L NaOH for 24 h, the ratio of sol. COD (SCOD) to total COD (TCOD) of the treated sludge increased from 2 to 81%, the av. mol. wt. was reduced from 31,000 to 8500 amu, and the total concn. of amino acids was significantly raised from 1.8 to 167.8 mg-N/L. Results of the 24-day **BMP** test showed that TCOD removal of the treated sludge increased from 35 to 51% and that methane prodn. was improved from 0.33 to 0.37 m3-CH4/kg-COD.

L21 ANSWER 5 OF 5 MEDLINE DUPLICATE 2
97114070 Document Number: 97114070. PubMed ID: 8955889. Identification and cloning of a novel type I **serine/threonine** kinase receptor of the TGF-beta/**BMP** superfamily in rat prostate. Kang Y; Reddi A H. (Department of Orthopaedic Surgery, Johns Hopkins Oncology Center, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.) BIOCHEMISTRY AND MOLECULAR BIOLOGY INTERNATIONAL, (1996 Nov) 40 (5) 993-1001. Journal code: BOD; 9306673. ISSN: 1039-9712. Pub. country: Australia. Language: English.

AB A cDNA clone encoding a new member of the type I **serine/threonine** kinase receptors of the TGF-beta/**BMP** superfamily was isolated from a rat prostate cDNA library. The predicted sequence of the encoded protein is 493 amino acids with a molecular weight of 55 kDa. It contains a putative **cysteine** rich extracellular domain, a transmembrane domain, a conserved type I receptor GS domain and a cytoplasmic **serine/threonine** kinase domain. The kinase domain shares 80% homology with that of ALK-4 and ALK-5 whose ligands are activin and TGF-beta. Northern blot analysis revealed that this prostate **serine/threonine** kinase receptor I (PSKR-I) is highly expressed in rat dorsolateral prostate, coagulating gland (anterior prostate), cerebellum and adipose tissue.

=> d his

(FILE 'HOME' ENTERED AT 19:28:44 ON 26 MAR 2002)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 19:29:10 ON 26 MAR 2002

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L1         78909 S TGF BETA
L2          3177 S L1 AND BONE MORPHOGENETIC PROTEIN
L3          2334 S L2 AND BMP
L4             0 S L3 AND "MP52"
L5            34 S L3 AND "GDF-5"
L6            17 DUP REMOVE L5 (17 DUPLICATES REMOVED)
L7             9 S L3 AND SUBSTITUTION
L8             5 DUP REMOVE L7 (4 DUPLICATES REMOVED)
L9            28 S L2 AND MONOMER
L10            1 S L9 AND AMINO ACID SUBSTITUTION
L11            0 S BMP SUBSTITUTION
L12        13924 S BMP
L13          199 S L12 AND CYSTEINE
L14            1 S L13 AND REPLACEMENT
L15            0 S L4 AND SERINE
L16            0 S L4 AND THREONINE
L17           27 S L13 AND SERINE
L18           13 S L17 AND THREONINE
L19            1 S L18 AND ALANINE
L20            7 DUP REMOVE L17 (20 DUPLICATES REMOVED)
L21            5 DUP REMOVE L18 (8 DUPLICATES REMOVED)
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=> s l13 and osteoporosis

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L22            1 L13 AND OSTEOPOROSIS
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=> d l22 cbib abs

L22 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2000:133721 Document No. 132:176643 Chordin-related proteins from human cDNA libraries. Jacobs, Kenneth; McCoy, John M.; Lavallie, Edward R.; Collins-Racie, Lisa A.; Merberg, David; Treacy, Maurice; Diblasio-Smith, Elizabeth; Widom, Angela (Genetics Institute, Inc., USA). PCT Int. Appl. WO 2000009551 A1 20000224, 106 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US18117 19990810. PRIORITY: US 1998-95880 19980810; US 1999-306111 19990506.

AB Three novel human chordin-related proteins and polynucleotides encoding them are disclosed. Nucleotide and amino acid sequences are reported for full-length clones isolated from human adult placenta and brain cDNA libraries; both proteins contain chordin **cysteine** repeats. The DW665_4 clone binds to bone morphogenetic protein (**BMP**) family members, inhibits **BMP** activity, induces axis duplication in Xenopus embryos, and is active in various assays for bone formation. Recombinant prodn. of the chordin-related proteins and their mature forms can be achieved by std. techniques, and the proteins have biol. activities useful for therapeutic applications.

=> s BMP-5
L23 230 BMP-5

=> s l23 and BMP-6
L24 90 L23 AND BMP-6

=> s l24 and BMP-7
L25 75 L24 AND BMP-7

=> s l25 and BMP-12
L26 1 L25 AND BMP-12

=> d l25 cbib abs

L25 ANSWER 1 OF 75 MEDLINE
2002154570 Document Number: 21883727. PubMed ID: 11886169. Bone morphogenetic proteins act synergistically with haematopoietic cytokines in the differentiation of haematopoietic progenitors. Detmer Kristina; Walker Anna N. (Division of Basic Medical Sciences, Mercer University School of Medicine, Macon, GA, 31207, USA.) CYTOKINE, (2002 Jan) 17 (1) 36-42. Journal code: 9005353. ISSN: 1043-4666. Pub. country: United States. Language: English.

AB We examined the effects of bone morphogenetic protein-2 (BMP-2), -3, -4, -5, -6, and -7 on the proliferation and differentiation of bone marrow CD34(+) haematopoietic progenitors in semi-solid medium. The BMPs had no effect on haematopoietic colony development when added to medium containing erythropoietin (Epo) or Interleukin-3 plus Epo. Synergistic effects with the haematopoietic cytokines stem cell factor (SCF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) were observed. In conjunction with GM-CSF and Epo, BMP-4 increased the number of both erythroid and granulocyte/monocyte colonies formed in semi-solid medium ($P<0.01$). No other BMP stimulated erythroid colony development under these conditions, while BMP-3, **BMP-7** ($P<0.01$), **BMP-5**, and **BMP-6** ($P<0.05$) stimulated granulocyte/monocyte colony formation. **BMP-7** acted synergistically with stem cell factor to increase granulocyte/monocyte

colony formation but not erythroid colony formation. The other BMPs did not affect either erythroid or granulocyte/monocyte colony development under these conditions. These results suggest that individual BMPs form part of the complement of cytokines regulating the development of haematopoietic progenitors, and in particular, point to a role for BMP-4 in the control of definitive, as well as embryonic erythropoiesis. Copyright 2002 Elsevier Science Ltd.

=> dup remove l25
PROCESSING COMPLETED FOR L25
L27 28 DUP REMOVE L25 (47 DUPLICATES REMOVED)

=> s l27 and bone
L28 28 L27 AND BONE

=> d l28 1-28 cbib abs

L28 ANSWER 1 OF 28 MEDLINE
2002154570 Document Number: 21883727. PubMed ID: 11886169. **Bone** morphogenetic proteins act synergistically with haematopoietic cytokines in the differentiation of haematopoietic progenitors. Detmer Kristina; Walker Anna N. (Division of Basic Medical Sciences, Mercer University School of Medicine, Macon, GA, 31207, USA.) CYTOKINE, (2002 Jan) 17 (1) 36-42. Journal code: 9005353. ISSN: 1043-4666. Pub. country: United States. Language: English.
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L28 ANSWER 2 OF 28 MEDLINE
2002144301 Document Number: 21862949. PubMed ID: 11874242. Differential temporal expression of members of the transforming growth factor beta superfamily during murine fracture healing. Cho Tae-Joon; Gerstenfeld Louis C; Einhorn Thomas A. (Department of Orthopedic Surgery, Boston University Medical Center, Massachusetts 02118, USA.) JOURNAL OF BONE AND MINERAL RESEARCH, (2002 Mar) 17 (3) 513-20. Journal code: 8610640. ISSN: 0884-0431. Pub. country: United States. Language: English.
AB Fracture healing is a unique postnatal repair process in which the events of endochondral and intramembranous **bone** formation follow a definable temporal sequence. The temporal patterns of messenger RNA (mRNA) expression for members of the transforming growth factor beta (TGF-beta) superfamily were examined over a 28-day period of fracture healing in mouse tibias. **Bone** morphogenetic protein 2 (BMP-2) and growth and differentiation factor 8 (GDF8) showed maximal expression on day 1 after fracture, suggesting their roles as early response genes in the cascade of healing events. Restricted expression of GDF8 to day 1, in

light of its known actions as a negative regulator of skeletal muscle growth, suggests that it may similarly regulate cell differentiation early in the fracture healing process. GDF5, TGF-beta2, and TGF-beta3 showed maximal expression on day 7, when type II collagen expression peaked during cartilage formation. In contrast, BMP-3, BMP-4, **BMP-7**, and BMP-8 showed a restricted period of expression from day 14 through day 21, when the resorption of calcified cartilage and osteoblastic recruitment were most active. TGF-beta1, **BMP-5** and **BMP-6**, and GDF10 were constitutively expressed from day 3 to day 21. However, during the same time period, GDF3, GDF6, and GDF9 could not be detected, and GDF1 was expressed at extremely low levels. These findings suggest that several members of the TGF-beta superfamily are actively involved in fracture healing and although they are closely related both structurally and functionally, each has a distinct temporal expression pattern and potentially unique role in fracture healing.

L28 ANSWER 3 OF 28 MEDLINE

2000458696 Document Number: 20400561. PubMed ID: 10942522. Osteogenic protein-1 differentially regulates the mRNA expression of **bone** morphogenetic proteins and their receptors in primary cultures of osteoblasts. Yeh L C; Unda R; Lee J C. (Department of Biochemistry, The University of Texas Health Science Center at San Antonio, TX 78229-3900, USA.. carolyeh@biochem.uthscsa.edu) . JOURNAL OF CELLULAR PHYSIOLOGY, (2000 Oct) 185 (1) 87-97. Journal code: HNB; 0050222. ISSN: 0021-9541. Pub. country: United States. Language: English.

AB The mRNA expression patterns of several **bone** morphogenetic proteins (BMPs) and their receptors (BMPRs) in long-term primary cultures of fetal rat calvaria (FRC) cells were examined by Northern analysis. Their temporal orders of expression were correlated with those of several biochemical markers characteristic of osteoblastic cell differentiation. Distinct temporal patterns of expression of BMPs and BMPRs during osteoblastic cell differentiation were observed. BMP-2 and **BMP-7** mRNA levels did not change significantly. BMP-4 mRNA expression increased and reached a peak prior to matrix formation. **BMP-5** mRNA expression increased during the mineralization phase and **BMP-6** mRNA expression increased throughout all phases of cell differentiation. Effects of **BMP-7** (Osteogenic Protein-1; OP-1) on the expression patterns of several other members of the BMP family and the receptors were also studied. OP-1 downregulated the BMP-4, -5, and -6 mRNA levels by a maximal of 2-fold, 1.5-fold, and 6-fold, respectively. OP-1 did not change significantly the OP-1 and BMP-2 mRNA expression. Of the three type I BMPR examined, OP-1 upregulated ActR-I and BMPR-IA mRNA expression slightly but with statistical significance. OP-1 downregulated BMPR-IB mRNA expression slightly. OP-1 upregulated BMPR-II mRNA expression by a maximum of 2-fold. Our findings demonstrate that OP-1 differentially regulates the mRNA expression of several related members of the BMP family and their receptors in osteoblasts. The observations suggest that OP-1 action on osteoblastic cells involves a complex regulation of gene expression of related members of the BMP family and their receptors in a cell differentiation stage dependent manner.

L28 ANSWER 4 OF 28 MEDLINE

2000165987 Document Number: 20165987. PubMed ID: 10701160. Expression of **bone** morphogenetic proteins and rat distal-less homolog genes following rat femoral fracture. Yaoita H; Orimo H; Shirai Y; Shimada T. (Department of Biochemistry and Molecular Biology, Nippon Medical School, Tokyo, Japan.) JOURNAL OF BONE AND MINERAL METABOLISM, (2000) 18 (2) 63-70. Journal code: DA5; 9436705. ISSN: 0914-8779. Pub. country: Japan. Language: English.

AB Expression of the genes encoding **bone** morphogenetic proteins (BMPs), BMP type IA receptor (BMPR-1A), and rat distal-less homolog (rDlx) was studied in **bone**, callus, and the surrounding soft tissue

following rat femoral closed fracture, using RT-PCR-based techniques. Before fracture, the genes encoding **BMP-5**, **BMP-6**, and BMPR-1A were found to be expressed in both **bone** and the surrounding soft tissue, whereas the BMP-2 gene was expressed only in **bone** and **BMP-7** was not expressed in either tissue. Expression of these genes was unaffected by fracture. The gene encoding BMP-4 was also expressed in both **bone** and the surrounding soft tissue before fracture. Moreover, although unchanged in **bone**, 6 h after fracture BMP-4 expression was increased tenfold in the surrounding soft tissue. The increased BMP-4 expression was transient and returned to prefracture levels within 72 h. Expression of rDlx was also increased in **bone** after fracture, but at later times than were observed with BMP-4: elevated rDlx expression was detected after 48 h and persisted for 30 days or more. No expression of rDlx was observed in the surrounding soft tissue before or after fracture. These findings indicate that BMP-4 and rDlx are selectively expressed following femoral fracture in the rat, and also suggest that they are involved in the formation of the callus at an early point during the postfracture healing of **bone**.

L28 ANSWER 5 OF 28 MEDLINE

2000127978 Document Number: 20127978. PubMed ID: 10660478. Lineage-restricted expression of **bone** morphogenetic protein genes in human hematopoietic cell lines. Detmer K; Steele T A; Shoop M A; Dannawi H. (Division of Basic Medical Sciences, Mercer University School of Medicine, Macon, GA 31207, USA.. detmer.k@gain.mercer.edu) . BLOOD CELLS, MOLECULES, AND DISEASES, (1999 Oct-Dec) 25 (5-6) 310-23. Journal code: B5A; 9509932. ISSN: 1079-9796. Pub. country: United States. Language: English.

AB To explore the possibility that **bone** morphogenetic proteins (BMPs) are autocrine/paracrine regulators of hematopoietic differentiation and function, we screened a panel of human cell lines encompassing the hematopoietic lineages for expression of members of this family of genes. Expression of BMP-2, BMP-4, **BMP-6**, **BMP-7**, Growth and Differentiation Factor-1 (GDF-1), Placental **Bone** Morphogenetic Protein (PLAB), and Transforming Growth Factor-beta3 (TGF-beta3) was detected in one or more cell lines. BMP-2, BMP-4, **BMP-7**, and TGF-beta3 expression was also found in normal hematopoietic tissue. Expression of **BMP-5** and BMP-8 was not seen. Lineage-restricted patterns of expression were found for BMP-4 (T-lymphoid), **BMP-7** (lymphoid), PLAB (macrophage/monocyte), and GDF-1 (myeloid). Expression of BMP-2, GDF-1, and PLAB could be modulated by treatment with differentiating agents. Marked variations in the levels of BMP-4, **BMP-7**, and PLAB expression were encountered, indicating that disorders in BMP signaling pathways may play a role in the development of hematopoietic neoplasia.

L28 ANSWER 6 OF 28 MEDLINE

2000057586 Document Number: 20057586. PubMed ID: 10591586. Alcohol inhibition of cell adhesion in BMP-treated NG108-15 cells. Wilkemeyer M F; Pajerski M; Charness M E. (Neurology Service, VA Boston Healthcare System, West Roxbury, Massachusetts 02132, USA.) ALCOHOLISM, CLINICAL AND EXPERIMENTAL RESEARCH, (1999 Nov) 23 (11) 1711-20. Journal code: 35X; 7707242. ISSN: 0145-6008. Pub. country: United States. Language: English.

AB BACKGROUND: The L1 cell adhesion molecule is expressed as alternatively spliced neuronal and nonneuronal isoforms. We have reported that in transfected fibroblasts, ethanol variably inhibits cell-cell adhesion mediated by the nonneuronal isoform of human L1. In contrast, ethanol consistently inhibits morphogenetic changes and cell-cell adhesion in NG108-15 cells treated with OP-1 (**BMP-7**), a powerful inducer of L1 and N-CAM gene expression. METHODS: All studies were performed by using NG108-15 cells cultured in serum-free medium. Cell morphology was assessed by a quantitative assay of cell clustering. Cell

adhesion was measured by a short-term re-aggregation assay, and isoforms of L1 were characterized by RT-PCR and sequencing. RESULTS: We show that ethanol inhibits the morphogenetic effects of BMP-2, BMP-4, **BMP-5**, and **BMP-6**, each of which increases the expression of L1 and N-CAM. Pretreatment of NG108-15 cells with 25-100 mM ethanol did not induce tolerance to ethanol's inhibition of OP-1 morphogenesis or cell-cell adhesion. Ethanol or anti-L1 Fab fragments partially inhibited cell-cell adhesion in OP-1-treated NG108-15 cells. The combination of ethanol and Fab fragments did not inhibit cell-cell adhesion more than Fab fragments alone. As in L1-transfected fibroblasts, a series of n-alcohols displayed a cutoff between butanol and pentanol for inhibition of cell-cell adhesion in OP-1-treated NG108-15 cells. RT-PCR and direct sequencing revealed that the neuronal isoform was the sole or predominant L1 isoform in OP-1-treated NG108-15 cells. CONCLUSIONS: These data suggest that ethanol inhibits cell-cell adhesion in OP-1-treated NG108-15 cells by interacting directly or indirectly with the neuronal isoform of L1.

L28 ANSWER 7 OF 28 MEDLINE

1999436207 Document Number: 99436207. PubMed ID: 10504300. Characterization of **bone** morphogenetic protein-6 signaling pathways in osteoblast differentiation. Ebisawa T; Tada K; Kitajima I; Tojo K; Sampath T K; Kawabata M; Miyazono K; Imamura T. (Department of Biochemistry, The Cancer Institute of JFCR, and Research for the Future Program, Japan Society for the Promotion of Science, Toshima-ku, Tokyo 170-8455, Japan.) JOURNAL OF CELL SCIENCE, (1999 Oct) 112 (Pt 20) 3519-27. Journal code: HNK; 0052457. ISSN: 0021-9533. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Bone** morphogenetic protein (**BMP**)-**6** is a member of the transforming growth factor (TGF)-(&bgr;) superfamily, and is most similar to **BMP-5**, osteogenic protein (OP)-1/**BMP-7**, and OP-2/BMP-8. In the present study, we characterized the endogenous **BMP-6** signaling pathway during osteoblast differentiation. **BMP-6** strongly induced alkaline phosphatase (ALP) activity in cells of osteoblast lineage, including C2C12 cells, MC3T3-E1 cells, and ROB-C26 cells. The profile of binding of **BMP-6** to type I and type II receptors was similar to that of OP-1/**BMP-7** in C2C12 cells and MC3T3-E1 cells; **BMP-6** strongly bound to activin receptor-like kinase (ALK)-2 (also termed ActR-I), together with type II receptors, i.e. BMP type II receptor (BMPR-II) and activin type II receptor (ActR-II). In addition, **BMP-6** weakly bound to BMPR-IA (ALK-3), to which BMP-2 also bound. In contrast, binding of **BMP-6** to BMPR-IB (ALK-6), and less efficiently to ALK-2 and BMPR-IA, together with BMPR-II was detected in ROB-C26 cells. Intracellular signalling was further studied using C2C12 and MC3T3-E1 cells. Among the receptor-regulated Smads activated by BMP receptors, **BMP-6** strongly induced phosphorylation and nuclear accumulation of Smad5, and less efficiently those of Smad1. However, Smad8 was constitutively phosphorylated, and no further phosphorylation or nuclear accumulation of Smad8 by **BMP-6** was observed. These findings indicate that in the process of differentiation to osteoblasts, **BMP-6** binds to ALK-2 as well as other type I receptors, and transduces signals mainly through Smad5 and possibly through Smad1.

L28 ANSWER 8 OF 28 MEDLINE

1998075906 Document Number: 98075906. PubMed ID: 9415424. Expression patterns of **bone** morphogenetic proteins (Bmps) in the developing mouse tooth suggest roles in morphogenesis and cell differentiation. Aberg T; Wozney J; Thesleff I. (Institute of Biotechnology, University of Helsinki, Finland.) DEVELOPMENTAL DYNAMICS, (1997 Dec) 210 (4) 383-96. Journal code: A9U; 9201927. ISSN: 1058-8388. Pub. country: United States. Language: English.

AB **Bone** morphogenetic proteins (BMP) are secretory signal molecules

which have a variety of regulatory functions during morphogenesis and cell differentiation. Teeth are typical examples of vertebrate organs in which development is controlled by sequential and reciprocal signaling between the epithelium and mesenchyme. In addition, tooth development is characterized by formation of mineralized tissues: the **bone**-like dentin and cementum as well as epithelially derived enamel. We have performed a comparative in situ hybridization analysis of the expression of six different Bmps (Bmp-2 to **Bmp**-**7**) starting from initiation of tooth development to completion of crown morphogenesis when dentine and enamel matrices are being deposited. Bmps-2, -4, and -7 were frequently codistributed and showed marked associations with epithelial-mesenchymal interactions. Their expression shifted between the epithelium and mesenchyme starting from the stage of tooth initiation. They were subsequently expressed in the enamel knot, the putative signaling center regulating tooth shape. Their expression domains prior to and during the differentiation of the dentine-forming odontoblasts and enamel-forming ameloblasts was in line with functions in regulation of cell differentiation and/or secretory activities of the cells. The expression of Bmp-3 was confined to mesenchymal cells, in particular to the dental follicle cells which give rise to the cementoblasts, forming the hard tissue covering the roots of teeth. **Bmp**-**5** was expressed only in the epithelial ameloblasts. It was upregulated as the cells started to polarize and intense expression continued in the secretory ameloblasts. **Bmp**-**6** was expressed only weakly in the dental mesenchyme during bud and cap stages. Our results are in line with regulatory functions of Bmps at all stages of tooth morphogenesis. Bmps-2, -4, and -7 are conceivably parts of signaling networks regulating tooth initiation and shape development. They as well as **Bmp**-**5** may be involved in the induction and formation of dentine and enamel, and Bmp-3 in the development of cementum. The remarkable overlaps in the expression domains of different Bmp genes may implicate functional redundancy and/or formation of active heterodimers between different BMPs.

L28 ANSWER 9 OF 28 MEDLINE

97390872 Document Number: 97390872. PubMed ID: 9247707. Expression of **bone** morphogenetic proteins of human neoplastic epithelial cells. Hatakeyama S; Gao Y H; Ohara-Nemoto Y; Kataoka H; Satoh M. (Department of Oral Pathology, School of Dentistry, Iwate Medical University, Japan.) BIOCHEMISTRY AND MOLECULAR BIOLOGY INTERNATIONAL, (1997 Jul) 42 (3) 497-505. Journal code: BOD; 9306673. ISSN: 1039-9712. Pub. country: Australia. Language: English.

AB **Bone** morphogenetic proteins (BMPs) are crucial factors of osteogenesis. We investigated the expressions of BMP subtypes in human salivary adenocarcinoma cell line (HSG-S8), tongue squamous cell (HSC-4) and gingival squamous cell (Ca9-22) carcinoma cell lines, gastric poorly differentiated adenocarcinoma cell (MNK45) and signet ring cell (KATOIII) carcinoma cell lines, rectal adenocarcinoma (RCM-1, RCM-2, and RCM-3), and thyroid (8505C) and bladder (T24) carcinoma cell lines by reverse transcription-polymerase chain reaction (RT-PCR). RT-PCR disclosed that BMP-1 was expressed in all cell lines examined, and BMP-2 was amplified in almost all cells except MKN45. Two squamous cell carcinomas, HSC-4 and Ca9-22, and KATOIII expressed only BMP-1 and BMP-2. MKN45 did not express BMP-2, but expressed **BMP**-**7** and weakly BMP-4 and **BMP**-**5**. In addition to the expression **BMP**-**7**, and HSG-S8 expressed **BMP**-**6**. These findings indicated that the neoplastic epithelial cells possessed a rather great potency to express BMP mRNAs. On the other hand, among these carcinoma cells, HSG-S8 solely induced **bone** in nude mouse tumors, and HSC-4 and KATOIII contained many calcified masses in tumors while the rest did not induce either.

L28 ANSWER 10 OF 28 MEDLINE

97078910 Document Number: 97078910. PubMed ID: 8919035. Heterodimeric **bone** morphogenetic proteins show enhanced activity in vitro and in

vivo. Israel D I; Nove J; Kerns K M; Kaufman R J; Rosen V; Cox K A; Wozney J M. (Genetics Institute, Cambridge, MA 02140, USA.) GROWTH FACTORS, (1996) 13 (3-4) 291-300. Journal code: AOI; 9000468. ISSN: 0897-7194. Pub. country: Switzerland. Language: English.

AB The **bone** morphogenetic proteins (BMPs), a subgroup of the TGF-beta gene super-family, are dimeric molecules involved in the growth, differentiation and repair of a wide variety of tissues. Based on the observation that several of the BMPs co-purify when isolated from bovine **bone** and that a pattern of co-localization exists during mouse embryogenesis, we co-expressed various combinations of BMPs in Chinese hamster ovary cells to test for possible heterodimer formation and activity. Transient co-expression of BMP-2 with either **BMP**-**5**, **BMP**-**6** or **BMP**-**7**, or BMP-4 transiently co-expressed with **BMP**-**7**, resulted in more BMP activity than expression of any single BMP. Stable cell lines were then made in order to purify and characterize co-expressed BMPs in more detail. Co-expression of BMP-2 with **BMP**-**7** yielded heterodimeric BMP-2/7 with a specific activity about 20-fold higher than BMP homodimers in an in vitro alkaline phosphatase induction assay. These heterodimers were also 5- to 10-fold more potent than BMP-2 in inducing cartilage and **bone** in an in vivo assay. Similar results were obtained with BMP-2/6 heterodimer. These experiments demonstrate the increased potency of several BMP heterodimers relative to BMP homodimers and support the hypothesis that such heterodimeric forms are likely to have natural biological functions.

L28 ANSWER 11 OF 28 MEDLINE

96254773 Document Number: 96254773. PubMed ID: 8661956. Subtle differences in the mitogenic effects of recombinant human **bone** morphogenetic proteins -2 to -7 on DNA synthesis on primary **bone** -forming cells and identification of BMP-2/4 receptor. Mayer H; Scutt A M; Ankenbauer T. (Gesellschaft fur Biotechnologische Forschung mbH, Braunschweig.) CALCIFIED TISSUE INTERNATIONAL, (1996 Apr) 58 (4) 249-55. Journal code: CGH; 7905481. ISSN: 0171-967X. Pub. country: United States. Language: English.

AB The **bone** morphogenetic proteins (BMPs) are a group of related proteins capable of inducing the formation of new cartilage and **bone**. We report here a direct comparison of members of the BMP family in their capability to induce DNA synthesis in **bone** cell cultures. The promotion of DNA synthesis was determined in periosteal cells and epiphyseal and sternal chondrocytes of embryonic chick. We demonstrate that structurally homologous BMP-2 and BMP-4 exhibit the highest specific activity in the three tested cell types, whereas **BMP**-**5**, **BMP**-**6** activity is moderately reduced in periosteal cells and highly reduced in epiphyseal and sternal chondrocytes. The specific activity of **BMP**-**7** is the lowest in the three tested cell cultures. Receptor binding characteristics demonstrate a binding of BMP-2 with high affinity (KD = 0.45 nM) on periosteal cells, and excess of TGF-beta 1 does not displace BMP-4 binding. Chemical cross-linking with iodinated BMP-2 generates an affinity complex of 90 kDa. These findings suggest the presence of a BMP-2/BMP-4 receptor that discriminates subtle differences in function among homologous members of the BMP family.

L28 ANSWER 12 OF 28 MEDLINE

94375533 Document Number: 94375533. PubMed ID: 8089189. Recombinant Vgr-1/**BMP**-**6**-expressing tumors induce fibrosis and endochondral **bone** formation in vivo. Gitelman S E; Kobrin M S; Ye J Q; Lopez A R; Lee A; Derynck R. (Department of Pediatrics, University of California at San Francisco 94143.) JOURNAL OF CELL BIOLOGY, (1994 Sep) 126 (6) 1595-609. Journal code: HMV; 0375356. ISSN: 0021-9525. Pub. country: United States. Language: English.

AB Members of the TGF-beta superfamily appear to modulate mesenchymal differentiation, including the processes of cartilage and **bone** formation. Nothing is yet known about the function of the TGF-beta-related

factor vgr-1, also called **bone** morphogenetic protein-6 (**BMP-6**), and only limited studies have been conducted on the most closely related factors **BMP-5**, osteogenic protein-1 (OP-1) or **BMP-7**, and OP-2. Because vgr-1 mRNA has been localized in hypertrophic cartilage, this factor may play a vital role in endochondral **bone** formation. We developed antibodies to vgr-1, and documented that vgr-1 protein was expressed in hypertrophic cartilage of mice. To further characterize the role of this protein in **bone** differentiation, we generated CHO cells that overexpressed recombinant murine vgr-1 protein. Western blot analysis documented that recombinant vgr-1 protein was secreted into the media and was proteolytically processed to yield the mature vgr-1 molecule. To assess the biological activity of recombinant vgr-1 in vivo, we introduced the vgr-1-expressing CHO cells directly into the subcutaneous tissue of athymic nude mice. CHO-vgr-1 cells produced localized tumors, and the continuous secretion of vgr-1 resulted in tumors with a strikingly different gross and histological appearance as compared to the parental CHO cells. The tumors of control CHO cells were hemorrhagic, necrotic, and friable, whereas the CHO-vgr-1 tumors were dense, firm, and fibrotic. In contrast with control CHO tumors, the nests of CHO-vgr-1 tumor cells were surrounded by extensive connective tissue, which contained large regions of cartilage and **bone**. Further analysis indicated that secretion of vgr-1 from the transfected CHO tumor cells induced the surrounding host mesenchymal cells to develop along the endochondral **bone** pathway. These findings suggest that endochondral **bone** formation.

L28 ANSWER 13 OF 28 MEDLINE

94103306 Document Number: 94103306. PubMed ID: 8276880. Regulation of neural cell adhesion molecule and L1 by the transforming growth factor-beta superfamily. Selective effects of the **bone** morphogenetic proteins. Perides G; Safran R M; Downing L A; Charness M E. (Department of Pathology, Harvard Medical School, Boston, Massachusetts 02115.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Jan 7) 269 (1) 765-70. Journal code: HIV; 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The transforming growth factor-beta (TGF-beta) superfamily plays a role in embryogenesis and regeneration. We have reported that osteogenic protein-1 (OP-1) promotes cell aggregation and induces the expression of the neural cell adhesion molecules N-CAM and L1 in proliferating neuroblastoma x glioma hybrid NG108-15 cells (Perides, G., Safran, R. M., Rueger, D. C., and Charness, M. E. (1992) Proc. Natl. Acad. Sci. U.S.A. 89, 10326-10330; Perides, G., Hu, G., Rueger, D. C., and Charness, M. E. (1993) J. Biol. Chem. 268, 25197-25205). Here we show that the structurally homologous **bone** morphogenetic proteins (BMP) BMP-2 and BMP-4 are 10-50-fold more potent in these actions than the subfamily comprising **BMP-5**, **BMP-6**, and OP-1 (**BMP-7**). In contrast, members of the TGF-beta subfamily, activin-A, inhibin-A, and 29 additional growth factors and cytokines did not induce N-CAM. The addition of serum to cells growing in serum-free medium caused a concentration-dependent increase in N-CAM and L1 expression; however, serum did not potentiate the induction of N-CAM and L1 by 40 ng/ml OP-1. These findings suggest the presence in NG108-15 cells of a BMP-2/BMP-4 receptor that discriminates subtle differences in structure among homologous members of the TGF-beta superfamily. An endogenous ligand for this receptor may be present in serum.

L28 ANSWER 14 OF 28 MEDLINE

92344843 Document Number: 92344843. PubMed ID: 1637554. The **bone** morphogenetic protein family and osteogenesis. Wozney J M. (Genetics Institute, Inc., Cambridge, MA 02140.) MOLECULAR REPRODUCTION AND DEVELOPMENT, (1992 Jun) 32 (2) 160-7. Ref: 27. Journal code: AN7; 8903333. ISSN: 1040-452X. Pub. country: United States. Language: English.

AB The BMPs (**bone** morphogenetic proteins) are a group of related proteins originally identified by their presence in **bone**

-inductive extracts of demineralized **bone**. By molecular cloning, at least six related members of this family have been identified and are called BMP-2 through **BMP**-7. These molecules are part of the TGF-beta superfamily, based on primary amino acid sequence homology, including the absolute conservation of seven cysteine residues between the TGF-betas and the BMPs. The BMPs can be divided into subgroups with BMP-2 and BMP-4 being 92% identical, and **BMP**-5, **BMP**-6, and **BMP**-7 being an average of about 90% identical. To examine the individual activities of these molecules, we are producing each BMP in a mammalian expression system. In this system, each BMP is synthesized as a precursor peptide, which is glycosylated, processed to the mature peptide, and secreted as a homodimer. These reagents have been used to demonstrate that single molecules, such as BMP-2, are capable of inducing the formation of new cartilage and **bone** when implanted ectopically in a rodent assay system. Whether each of the BMPs possesses the same inductive activities in an animal is the subject of ongoing research. Based on the chondrogenic and osteogenic abilities of the BMPs in the adult animal, the expression of the mRNAs for the BMPs has been examined in the development of the embryonic skeleton by in situ hybridization. These studies demonstrate that the BMP mRNAs are spatially and temporally expressed appropriately for the proteins involved in the induction and development of cartilage and **bone** in the embryonic limb bud.(ABSTRACT TRUNCATED AT 250 WORDS)

L28 ANSWER 15 OF 28 MEDLINE

92320595 Document Number: 92320595. PubMed ID: 1820688. The DVR gene family in embryonic development. Lyons K M; Jones C M; Hogan B L. (Department of Cell Biology, Vanderbilt University Medical School, Nashville, TN 37232.) TRENDS IN GENETICS, (1991 Nov-Dec) 7 (11-12) 408-12. Ref: 31. Journal code: WEK; 8507085. ISSN: 0168-9525. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The DVR gene family consists of at least 15 members, including decapentaplegic from Drosophila, Xenopus Vg1 and the mammalian **bone** morphogenetic protein genes, encoding secreted proteins closely related to transforming growth factor beta Genetic and biochemical evidence supports the idea that DVR proteins form part of a cascade of extracellular signalling molecules mediating inductive tissue interactions during development.

L28 ANSWER 16 OF 28 MEDLINE

91346756 Document Number: 91346756. PubMed ID: 2491264. **Bone** morphogenetic proteins. Wozney J M. (Genetics Institute, Inc., Cambridge, MA 02140.) PROGRESS IN GROWTH FACTOR RESEARCH, (1989) 1 (4) 267-80. Ref: 68. Journal code: A6S; 8912757. ISSN: 0955-2235. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Bone** Morphogenetic Protein (BMP) refers to an activity derived from **bone** that induces the formation of cartilage and **bone** in vivo. This activity leads to a series of developmental processes including chemotaxis, proliferation, and differentiation, which result in the transient formation of cartilage and the production of living **bone** tissue, complete with hematopoietic marrow. The determination of the factor or factors responsible for this activity has clear significance both for our understanding of **bone** biology and for the clinical application of cartilage and **bone** replacement. Several newly discovered factors, BMP-1, BMP-2 (BMP-2A), BMP-3 (osteogenin), BMP-4 (BMP-2B), **BMP**-5, **BMP**-6, **BMP**-7, and osteoinductive factor (OIF) have been implicated in the BMP process. BMP-2 through **BMP**-7 are all in the TGF-beta superfamily of molecules, and are closely related to two factors (Vg1 and dpp) which are involved in a variety of developmental processes during embryogenesis. A recently discovered factor, OIF, exhibits BMP activity only in the presence of TGF-beta. BMP-2, expressed as a recombinant protein, is the only molecule described to data that has been shown to clearly induce by itself the

entire cartilage and **bone** formation process seen with **bone**-derived BMP. Evidence is accumulating that the BMP effect is a result of the combined actions of a set of BMP-2-like molecules. Definitive examination of the activities of the other factors will require expression of the recombinant proteins and testing of these in vivo alone and in combinations.

L28 ANSWER 17 OF 28 MEDLINE
91088608 Document Number: 91088608. PubMed ID: 2263636. Identification of transforming growth factor beta family members present in **bone** -inductive protein purified from bovine **bone**. Celeste A J; Iannazzi J A; Taylor R C; Hewick R M; Rosen V; Wang E A; Wozney J M. (Genetics Institute, Inc., Cambridge, MA 02140.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1990 Dec) 87 (24) 9843-7. Journal code: PV3; 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.
AB Characterization of the polypeptides present in **bone**-inductive protein extracts from bovine **bone** has led to the cloning of seven regulatory molecules, six of which are distantly related to transforming growth factor beta. The three human **bone** morphogenetic proteins (BMPs) we describe herein, **BMP-5** , **BMP-6**, and **BMP-7**, show extensive sequence similarity to BMP-2, a molecule that by itself is sufficient to induce de novo **bone** formation in vivo. The additive or synergistic contribution of these BMP-2-related molecules to the osteogenic activity associated with demineralized **bone** is strongly implicated by the presence of these growth factors in the most active fractions of highly purified **bone** extract.

L28 ANSWER 18 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2001:574325 Document No.: PREV200100574325. **Bone** morphogenetic protein (BMP) expression is altered by spinal cord injury in rats. Benton, R. L. (1); Darnall, J. B. (1); Whittemore, S. R. (1). (1) Dept Neurological Surgery, Univ Louisville, Louisville, KY USA. Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2032. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001 ISSN: 0190-5295. Language: English. Summary Language: English.
AB **Bone** morphogenetic proteins (BMPs) are members of the TGF-beta superfamily of cytokines and have been shown to be crucial for normal CNS development. Specifically, BMPs appear to be potent inducers of gliogenesis, as determined by both in vitro and in vivo studies. Studies from our laboratory demonstrate that pluripotent cells engrafted into the injured spinal cord are restricted to glial lineage despite neurogenic potential in vitro (Cao et al., Exp. Neurol., 2001, 167:48-58). We hypothesized that altered BMP or BMP receptor expression could underlie the lack of neuronal differentiation observed in this study. Female Fisher 344 rats were subjected to a moderate contusion injury at the T10 spinal level. One week following SCI, RNA was prepared tissue at the injury epicenter as well as time/spatially matched intact spinal cord. Total RNA was then reverse transcribed, and subjected to PCR analysis using specific primers for BMP-2-7, 9, and 11-13 as well as BMP receptor subunits 1a, 1b, and 2. In the normal spinal cord, mRNA for BMP 2-6, BMP-9, BMP-12 (GDF-7), and BMP-13 (GDF-6) was detectable. In addition, mRNA for all three BMP receptor subunits was detected. In contrast, mRNA for **BMP-** **7** (OP-1) and BMP-11 was not observed in the normal adult spinal cord. Preliminary data suggests that BMP2-4 and BMP-12 mRNA expression is induced by SCI with no apparent alteration in the expression profile of other BMPs observed in the spinal cord. Studies are currently ongoing to provide quantitative data pertaining to these observations as well to determine the spatio-temporal distribution of altered BMP expression.

L28 ANSWER 19 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2001:121703 Document No.: PREV200100121703. Developmental expression patterns of **bone** morphogenetic proteins, receptors, and binding proteins

in the chick retina. Belecky-Adams, Teri; Adler, Ruben (1). (1) Johns Hopkins School of Medicine, 600 N. Wolfe Street, 519 Maumenee, Baltimore, MD, 21287-9257: radler@jhmi.edu USA. Journal of Comparative Neurology, (February 19, 2001) Vol. 430, No. 4, pp. 562-572. print. ISSN: 0021-9967. Language: English. Summary Language: English.

AB **Bone** morphogenetic proteins (BMPs), a large subfamily of the transforming growth factor-beta (TGF-beta) superfamily of growth factors, have been implicated in patterning of the central nervous system, but their role in the retina is much less well known. As an initial step in addressing this issue, we have investigated by in situ hybridization the expression patterns of BMP-2, -4, -5, -6, and -7, BMP receptor kinases (BRKs) -1, -2, and -3, and BMP binding proteins noggin and chordin, in the chick embryonic eye at embryonic day 3 (E3), and in isolated retinas at E6, E8, and E18. Strikingly, all mRNAs examined had spatially restricted patterns of expression in the early eye, with the receptors found primarily in the ventral portion of the retina and in the optic stalk, and the ligands and binding proteins localized to other regions of the retina and/or retinal pigment epithelium. Dorso-ventrally restricted patterns of expression persisted at E8, but were no longer apparent at E18, whereas layer-specific patterns of expression were detectable at both E8 and E18. This distribution of BMP family members, receptors, and binding proteins within the retina appears consistent with a possible role in patterning and/or differentiation of this tissue.

L28 ANSWER 20 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2001:97169 Document No.: PREV200100097169. Specific receptors for **bone** morphogenetic protein-7/osteogenic protein-1 in rat and human brain. Dattatreyamurty, B. (1); Roux, E. C.; Higgins, D. M.; Kaplan, P. L.. (1) Creative BioMolecules, Inc., Hopkinton, MA USA. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-412.3. print. Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience. ISSN: 0190-5295. Language: English. Summary Language: English.

AB BMPs regulate elaboration and maintenance of dendritic arbors in and promote survival of many types of neurons, and enhance recovery from stroke. The molecular events involved in **BMP-7** action on brain are not understood. **BMP-7** is found in normal mammalian CSF and, unlike other neurotrophic factors, is present at concentrations sufficient to elicit a biological response. When adult rats received a single intracisternal injection of 125I-labeled **BMP-7**, uptake by brain and spinal cord peaked at 13% and 2% of the injected dose, respectively, by 3 hours post-injection. Plasma membranes isolated from brain exhibited specific and saturable binding of 125I-labeled **BMP-7**. The binding of labeled **BMP-7** was inhibited by unlabeled **BMP-7** in a dose-dependent manner. IGF-1, PDGF, EGF, bFGF, TGF-alpha &-beta, activin-A and inhibin-A and B, as well as other members of BMP family such as BMP-2 and CDMP-1/GDF-5 failed to inhibit the binding of labeled **BMP-7** to rat and human brain receptors. **BMP-5** and **BMP-6**, which show 88% and 87% sequence homology with **BMP-7**, respectively, strongly competed with **BMP-7** for binding to human brain receptors. Scatchard analysis indicated that the **BMP-7** receptors in rat and human brain each contained a single class of high affinity binding sites for **BMP-7**. The Ka for **BMP-7** binding to receptors in rat and human brains were 2.18 x 109 M-1 and 1.09 x 109 M-1, with binding capacities of 0.55 and 0.367 pmol/mg plasma membrane protein, respectively. Ligand- and western-blot analysis of human brain plasma membranes showed the presence of a specific **BMP-7** binding component that may be a long form of BMP type II receptor with a relative molecular mass of 100 kDa.

L28 ANSWER 21 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1994:382851 Document No.: PREV199497395851. Human **bone** morphogenetic proteins (BMP-2, BMP-4, **BMP-5**, **BMP-6**

and **BMP**-7) induce differentiation into three mesenchymal cell lineages. Ahrens, M. (1); Hollnagel, A.; Schroeder, D.; Mayer, H.; Gross, G.. (1) Gesellschaft Biotechnologische Forschung, Mascheroder Weg 1, 38124 Braunschweig Germany. Bone and Mineral, (1994) Vol. 25, No. 1, pp. S3-S4. Meeting Info.: Fifth Workshop on Cells and Cytokines in Bone and Cartilage Davos, Switzerland April 11-13, 1994 ISSN: 0169-6009. Language: English.

L28 ANSWER 22 OF 28 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1994:325433 Document No.: PREV199497338433. Human **bone** morphogenetic proteins (BMP-2, BMP-4, **BMP**-5, **BMP**-6 and **BMP**-7) induce differentiation into three mesenchymal cell lineages. Hollnagel, A.; Ahrens, M.; Schroeder, D.; Mayer, H.; Gross, G.. Gesellschaft Biotechnol. Forschung, (GBF), Mascheroder Weg 1, 38124 Braunschweig Germany. European Journal of Cell Biology, (1994) Vol. 63, No. SUPPL. 40, pp. 35. Meeting Info.: Annual Meeting of the Deutsche Gesellschaft fuer Zellbiologie (German Society for Cell Biology) Luebeck, Germany March 20-24, 1994 ISSN: 0171-9335. Language: English.

L28 ANSWER 23 OF 28 SCISEARCH COPYRIGHT 2002 ISI (R)
1999:939414 The Genuine Article (R) Number: 260PF. Lineage-restricted expression of **bone** morphogenetic protein genes in human hematopoietic cell lines. Detmer K (Reprint); Steele T A; Shoop M A; Dannawi H. MERCER UNIV, SCH MED, DIV BASIC MED SCI, 1550 COLL ST, MACON, GA 31207 (Reprint); MED CTR CENT GEORGIA, DEPT PEDIAT, MACON, GA. BLOOD CELLS MOLECULES AND DISEASES (15 NOV 1999) Vol. 25, No. 21, pp. 310-323. Publisher: ACADEMIC PRESS INC. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 1079-9796. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB To explore the possibility that **bone** morphogenetic proteins (BMPs) are autocrine/paracrine regulators of hematopoietic differentiation and function, we screened a panel of human cell lines encompassing the hematopoietic lineages for expression of members of this family of genes. Expression of BMP-2, BMP-4, **BMP**-6, **BMP**-7, Growth and Differentiation Factor-1 (GDF-1), Placental **Bone** Morphogenetic Protein (PLAB), and Transforming Growth Factor-beta 3 (TGF-beta 3) was detected in one or more cell lines. BMP-2, BMP-1, **BMP**-7, and TGF-beta 3 expression was also found in normal hemaropoietic tissue. Expression of **BMP**-5 and BMP-S was not seen. Lineage-restricted patterns of expression were found for BMP-4 (T-lymphoid), **BMP**-7 (lymphoid), PLAB (macrophage/monocyte), and GDF-1 (myeloid), Expression of BMP-2, CDF-1, and PLAB could be modulated by treatment with differentiating agents. Marked variations in the levels of BMP-4, **BMP**-7, and PLAB expression were encountered, indicating that disorders in BMP signaling pathways may play a role in the development of hematopoietic neoplasia.

L28 ANSWER 24 OF 28 CAPLUS COPYRIGHT 2002 ACS
2002:10295 Document No. 136:74707 **Bone** protein mixtures for wound healing. Akella, Rama; Ranieri, John P. (Sulzer Biologics Inc., USA). PCT Int. Appl. WO 2002000244 A2 20020103, 61 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US41110 20010622. PRIORITY: US 2000-605266 20000628.
AB A protein mixt. that is useful in the treatment of wounds, where the mixt. is isolated from **bone** or is produced from recombinant proteins and may include two or more of BMP-2, BMP-3, BMP-4, **BMP**-5, **BMP**-6, **BMP**-7, TGF-.beta.1, TGF-.beta.2, TGF-.beta.3, and FGF-1. A single dose application of **bone** protein was effective in reducing the healing time of full thickness wound in nude mice grafted with human meshed split thickness skin. Addnl., the thickness of neodermis and the d. of the capillaries in the treated wounds were significantly higher

compared to the control groups.

L28 ANSWER 25 OF 28 CAPLUS COPYRIGHT 2002 ACS
1999:736893 Document No. 131:332976 Sustained dna delivery from structural porous matrices for gene therapy applications with special emphasis is on **bone** formation and regeneration. Shea, Lonnie D.; Bonadido, Jeffrey; Mooney, David J. (The Regents of the University of Michigan, USA). PCT Int. Appl. WO 9958656 A2 19991118, 144 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BJ, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US10330 19990512. PRIORITY: US 1998-PV85305 19980513; US 1998-PV109054 19981119.

AB Disclosed are particular 3-dimensional structural matrixes contg. DNA and their use in the prolonged release of DNA in various biol. environments. The structural matrix is a porous polymer [PLGA]-based contg. pores formed by gas foaming involving inert gases (CO2) and leaching out of a water-sol. particulate (salt, NACL, sugar, glucose, sucrose, mannitol) when exposed to body fluids. The admixt. is compression molded into a selected size and shape prior to executing the gas foaming process. The structural matrix may also be an alginate or modified alginate matrix. This structural matrix is a biocompatible or biodegradable matrix. It may also be a lactic acid polymer, glycolic acid polymer or lactic acid/glycolic acid copolymer matrix. At least part of this matrix may be comprised of lactic acid/glycolic acid (PLGA) copolymer matrix. The structural matrix may be modified where one side section is bonded to one cell interaction mol. such as cell adhesion mols., cell attachment peptides, proteoglycan attachment peptide sequences, proteoglycans, cell adhesion polysaccharides, growth factors, cell adhesion enzymes, RGD peptide, fibronectin, vitronectin, Laminin A, Laminin B1, Laminin B2, collagen 1 and thrombospondin. The DNA-matrix materials are created such that they maintain a defined space, allowing cellular migration, transfection and proliferation to occur in a controlled manner. Such DNA-contg. structural matrixes are thus particularly useful in in vivo cell transfection and gene expression in the context of gene therapy. This may encode a protein for stimulating **bone** progenitors or wound healing in fibroblast or in tissue or organ regeneration or transplantation or an antigen for immunity or cytotoxic or apoptosis-inducing protein or a transcription factor or elongation factor or cell cycle control protein or kinase or phosphatase or DNA repair protein or oncogene or tumor suppressor or angiogenic protein or anti-angiogenic protein or immune response stimulating protein or cell surface receptor or accessory signaling mol. or transport protein or anti-bacterial or anti-viral protein or hormone or neurotransmitter or growth factor or growth factor receptor or interferon or interleukin or chemokine or cytokine or colony stimulating factor or chemotactic factor protein of growth hormone or parathyroid hormone or PTH1-34 polypeptide or **bone** morphogenic protein or BMP-2A or BMP-2B or BMP-3 or BMP-4 or **BMP-5** or **BMP-6** or **BMP-7** or BMP-8 or TGF-.alpha. or TGF-.beta.1 or TGF-.beta.2 or latent TGF.beta. binding protein or activin/inhibin protein or FGF or GMCSF or EGF or PDGF or insulin-like growth factor or leukemia inhibitory factor. This method allows for the use in gene transfer to cells within a tissue site and in manuf. of a medicament for gene therapy. Implantable medical devices comprising this gene-matrix are described. The release of nucleic acids from the matrix is controlled by diffusion. This method also applies to cancer therapy or treating viral infection.

L28 ANSWER 26 OF 28 CAPLUS COPYRIGHT 2002 ACS
1998:331558 Document No. 129:32361 Neural regeneration using human **bone** morphogenetic proteins. Wang, Elizabeth A.; D'Alessandro,

Josephine S.; Toriumi, Dean M. (Genetics Institute, Inc., USA). U.S. US 5756457 A 19980526, 7 pp., Cont.-in-part of U.S. Ser. No. 112,492, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1995-435120 19950505. PRIORITY: US 1993-112492 19930826.

AB A device for inducing growth of neural cells and repairing neural defects in a mammal comprises tubing or a stent (as an artificial nerve replacement vessel) contg. a suitable matrix (e.g. a collagen sponge) on which a **bone** morphogenetic protein (BMP) is adsorbed. The device is implanted at a site of neural defect, damage, or depletion in need of peripheral nerve repair. Suitable BMPs are BMP-2, BMP-4, **BMP-5**, **BMP-6**, **BMP-7**, and heterodimers of BMP-2/6 and BMP-2/7. Thus, serum-free mouse embryo Balb/c cells treated with recombinant human BMP-2 at 10 ng/mL differentiated morphol. into astrocyte-like cells and expressed glial fibrillary acidic protein, a specific marker of astrocytes; astrocytes provide a conducive environment for axon growth. In rats with severed sciatic nerves, stents contg. a collagen sponge impregnated with recombinant human BMP-2 were anastomosed to the severed ends of the nerve; observation of compd. muscle action potentials 6-12 wk later indicated nerve regeneration and restoration of function, which was confirmed microscopically.

L28 ANSWER 27 OF 28 CAPLUS COPYRIGHT 2002 ACS

1993:464927 Document No. 119:64927 Recombinant **bone** morphogenetic protein heterodimers and their manufacture with transgenic cells. Israel, David; Wolfman, Neil M. (Genetics Institute, Inc., USA). PCT Int. Appl. WO 9309229 A1 19930513, 168 pp. DESIGNATED STATES: W: AU, BR, CA, FI, HU, JP, KR, NO, RU; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US9430 19921102. PRIORITY: US 1991-787496 19911104; US 1992-864692 19920407.

AB A method for producing heterodimeric **bone** morphogenetic proteins (BMPs) comprises culturing a transgenic cell expressing 2 different BMP genes and isolating the heterodimeric BMP from the medium. CHO cells cotransfected with plasmids encoding BMP-2 or BMP-4 and with plasmids encoding **BMP-5**, **BMP-6**, or **BMP-7** produced heterodimeric BMPs. These heterodimers stimulated W20 cells to produce more alk. phosphatase activity than did the individual BMP homodimers or mixts. of homodimers. The heterodimers also preformed better in an in vivo test, the rat ectopic **bone** formation assays.

L28 ANSWER 28 OF 28 CAPLUS COPYRIGHT 2002 ACS

1991:201139 Document No. 114:201139 Recombinant human **bone** morphogenetic proteins and their pharmaceutical use. Wang, Elizabeth A.; Wozney, John M.; Rosen, Vickie A.; Celeste, Anthony J. (USA). PCT Int. Appl. WO 9011366 A1 19901004, 97 pp. DESIGNATED STATES: W: AU, CA, JP, KR; RW: AT, BE, CH, DK, ES, FR, GB, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1990-US1630 19900327. PRIORITY: US 1989-329610 19890328; US 1989-347559 19890504; US 1989-370544 19890623; US 1989-370547 19890623; US 1989-370549 19890623; US 1989-437409 19891115; US 1989-438919 19891117; US 1990-490033 19900307.

AB Recombinant human **bone** morphogenetic proteins (BMPs) **BMP-5**, **BMP-6**, and **BMP-7** are produced. These proteins may be used to treat cartilage and **bone** defects or for wound healing or tissue repair. Bovine **BMP-5** was purified and oligonucleotide probes based on the amino acid sequence were prepd. and used to isolate bovine **BMP-5** and **BMP-6** cDNA. This cDNA was used to screen a human cDNA bank and identify **BMP-5**, **BMP-6**, and **BMP-7** cDNA clones. Expression vectors for the 3 BMPs were constructed and the proteins were produced in CHO cells.

=> s human MP52 dimer

L29 1 HUMAN MP52 DIMER

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L29 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
1996:732173 Document No. 126:1703 Recombinant preparation of dimeric human protein MP52 and use for treating bone diseases. Makishima, Fusao; Takamatsu, Hiroyuki; Miki, Hideo; Kawai, Shinji; Kimura, Michio; Matsumoto, Tomoaki; Katsuura, Mieko; Enomoto, Koichi; Satoh, Yusuke (Hoechst Japan Limited, Japan; Makishima, Fusao; Takamatsu, Hiroyuki; Miki, Hideo; Kawai, Shinji; Kimura, Michio; Matsumoto, Tomoaki; Katsuura, Mieko; Enomoto, Koichi; Satoh, Yusuke). PCT Int. Appl. WO 9633215 A1 19961024, 33 pp. DESIGNATED STATES: W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1996-JP1062 19960419. PRIORITY: JP 1995-93664 19950419; JP 1995-322403 19951117.

AB Methods for recombinant prepn. of mature monomeric human protein MP52 (119 amino acids) in transgenic Escherichia coli followed by chem. dimerization of the protein are disclosed. Biol. effects of the dimer on stimulating the growth of bones or cartilage were also demonstrated. This dimer protein is useful in the treatment of cartilage and bone diseases.

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